EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Welcome and Overview

International Workshop on ethical and GCP aspects of the acceptance of clinical trials submitted in Marketing Authorisation Applications to EMA.

EMA, London 6-7 September 2010.

Noel Wathion, Head, Patient Health Protection,
European Medicines Agency

Welcome to Stakeholders

Civil society:

- Patients representatives from all continents
- NGOs

Clinical Trial Sponsors and MAHs:

- Pharmaceutical Industry Associations
- CROs
- Academic sponsors

Regulators including clinical assessors, GCP inspectors:

- Regulatory authority partners from all continents
- EU National Competent Authorities and EMA, its Scientific Committees and working groups
- Ethics committees

International organisations

- WHO, WMA, CIOMS Council of Europe, EDCTP

Experts

Press

What are the challenges?

- Globalisation of clinical research
- Reaching a common understanding and framework for ethical and scientific standards
- Achieving a strong regulatory and ethical framework in all countries where clinical trials are conducted
- Assistance through sharing of expertise and capacity building
- Role of Regulatory Authorities through global regulatory network

Workshop - context

Draft Reflection paper:

- Undergoing public consultation until 30 Sep 2010 – written submissions are requested.
- Worskhop is part of consultation process
- Summary report of workshop, slides and list of attendees – to be published by end of Oct 2010
- Written submissions to the Consultation process to be published by end of 2010
- Draft reflection paper to be revised, reviewed, finalised and published - target mid 2011.
- Implementation of the practical actions set out, and further development of policy and processes where needed.

Purpose of workshop

- Consult
- Listen
- Identify areas of consensus
- Discuss areas of divergence
- Identify the limits and the possibilities of the current frameworks
- Be practical – what we can implement in current framework
- Be ambitious – identify objectives for further development
- Most of all – work together, internationally, as partners, to help complete the global framework for clinical trials

Thank you

EUROPEAN MEDICINES AGENCY
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Background and Objectives – how did we get here and where are we going?

International Workshop on acceptance of clinical trials – ethical and GCP aspects, 6-7 September 2010, EMA, London.

Fergus Sweeney, Head, Compliance and Inspections,
European Medicines Agency

What are the issues?

Acceptability

- Ethical requirements
- Data quality

Focus of workshop

Applicability

- to EU population
- to EU medical practice

The Dilemna……

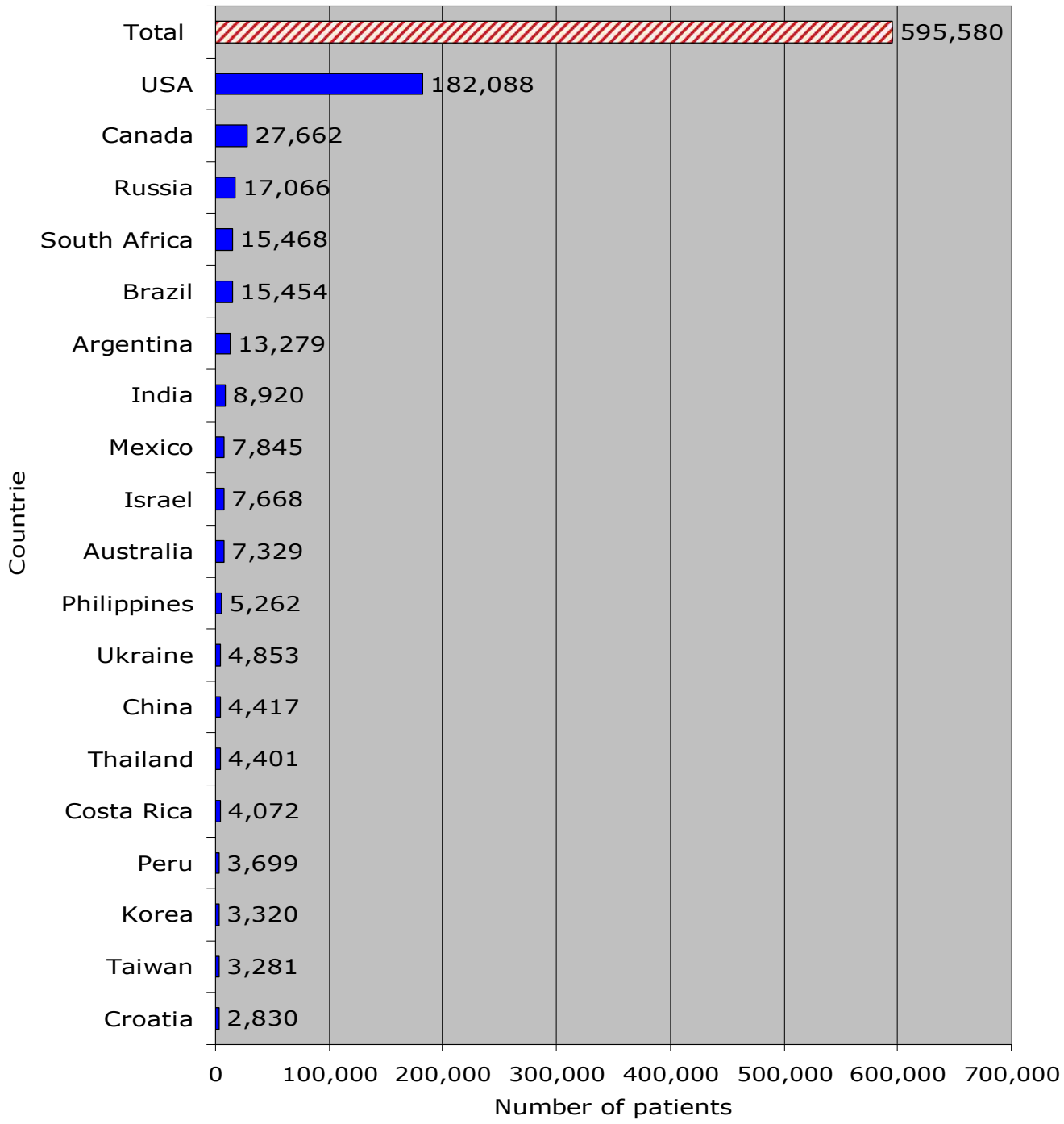
Between 2005 and 2009

- **595,580** Patients in pivotal trials

  (38.8% in Europe, 35.2% in North America, 3.0% Africa, 9.3% Middle East/Asia Pacific, 3.8% CIS, 9.2%Latin America)

- **44,034** clinical trial sites in **89** countries

- **347 new** MAA applications, **152** GCP inspections


Total
595,580
USA
182,088
Canada
27,662
Russia
17,066
South Africa
15,468
Brazil
15,454
Argentina
13,279
India
8,920
Mexico
7,845
Israel
7,668
Australia
7,329
Philippines
5,262
Ukraine
4,853
China
4,417
Thailand
4,401
Costa Rica
4,072
Peru
3,699
Korea
3,320
Taiwan
3,281
Croatia
2,830
Countrie
0
100,000
200,000
300,000
400,000
500,000
600,000
700,000
Number of patients

….The Dilemna

Wherever in the world we stand, the majority of clinical trials are conducted somewhere else:

- Under a different regulatory framework
- In a different culture

Each of us relies on the same trials to make decisions to allow or disallow, to use or not to use a medicine.

- Decisions by regulators
- Decisions by patients and by their health care providers

Directive 2001/83/EC

- regulatory requirements for MAAs submitted to EU

"..it should be **verified**, at the **time of the evaluation of the application for authorisation**, that these **trials were conducted in accordance** with the principles of **good clinical practice** and the **ethical requirements equivalent** to the provisions of that Directive."

"..shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. **They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki**."

MAH statement that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

Reflection paper on ethical and GCP aspects of clinical trials conducted in third countries for evaluation in marketing authorisation applications for medicines for human use, submitted to the EMA.

Drafted by EMA Working group – members from CHMP/COMP/PDCO, PCWP, HCPWP, GCP IWG

Objectives of the Working group:

- To draft the reflection paper
- Based on existing initiatives, legislation and international guidance
- Set out EMA understanding of these requirements
- Define practical actions that can be implemented
- Make expectations clear to clinical trial sponsors
- Cover complete life cycle of product - from trial design, to improved MAAs evaluation, enhanced transparency, and international cooperation

Draft Reflection Paper contents:

Topic 1. Clarify the practical application of ethical standards for clinical trials, in the context of EMEA activities

Topic 2. Determine the practical steps to be undertaken during the provision of guidance and advice in the drug development phase

Topic 3. Determine the practical steps to be undertaken during the Marketing Authorisation phase

Topic 4. International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area

Goals

Subjects/patients participating in trials are fully protected – wherever the trial takes places

Availability of safe and effective new medicines, as early as possible, with data relevant to all regions

Thank you - Questions

Reflection Paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries: Canada's Perspective

International Workshop
EMA, London, September 6-7, 2010

Santé Canada Health Canada

General Impressions

- Agreement that international cooperation is necessary to effectively and efficiently regulate international clinical trials
- Recognition that this cooperation can reduce duplication of efforts and improve scope of oversight
- Interest in establishing a framework for knowledge sharing and identifying points of contact

Opportunities

- Identifying “best practices” in GCP inspection programs for the purpose of local improvement and international confidence-building
- Increased involvement in identifying priority areas could facilitate the development of regulatory frameworks in areas where they are most needed

Challenges

- Current regulatory frameworks and absence of formal processes for sharing information may limit the type or amount of information which can be shared between regulatory authorities
- Resources required to conduct foreign inspections may be limiting where there is no cost-recovery for GCP inspections in place
- Global nature of clinical trials involves many layers of regulation and parties involved, and the need to consider differences in local practices and requirements

International Harmonization and Cooperation

- Canada adopted the International Conference on Harmonization Topic E6 in 1997; this guidance supports and provides interpretation to the Regulations governing clinical trials conducted in Canada, which came into force in 2001.
- Implementation Plan for Regulatory Co-operation on Medicinal Products between the EU and Health Canada (April 2009)
- Memorandum of Understanding with US FDA (since 2003)

Current activities and initiatives

- Observation, when possible, of foreign inspections conducted in Canada
- Participation in international working groups and inspector training
- Health Canada's International Forum provides information and guidance to countries with developing regulatory frameworks
- Modernization of existing legislation to correspond with the changing health product regulatory landscape and clarify regulatory requirements

Thank you!

Candice Hilder

A/Coordinator

GCP Compliance Unit

Health Products and Food Branch Inspectorate

Health Canada

Overview of reflection paper

Jin-Ju Li
State Food Administration
China

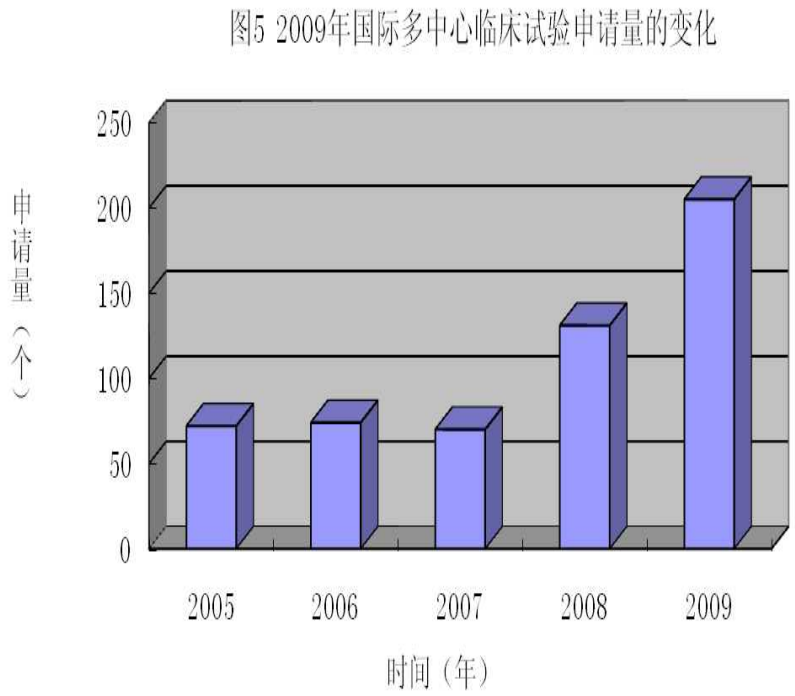
Sept.2010
London

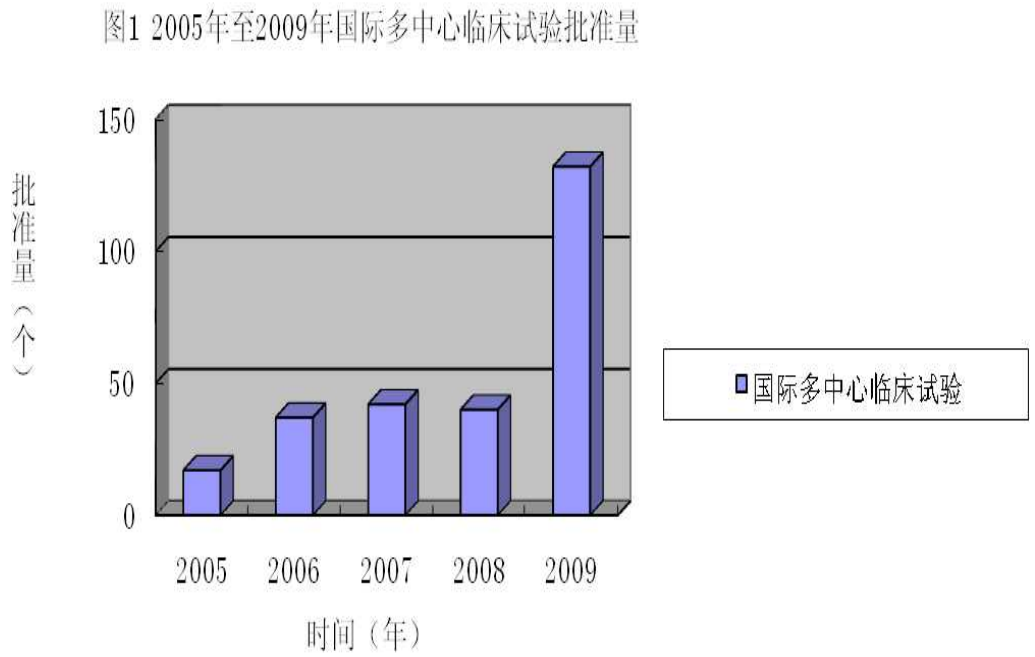
Overview of Reflection Paper

- **Structure clear**
- **Content complete and specific**
- **Significance**
  - ***Enhance the protection of subject's health, right and welfare in clinical trial conducted in the third countries***
  - ***Improve the quality of clinical trials conducted in the third countries***
  - ***Strengthen international cooperation among EAM and NRAs on regulation of clinical trials***

Increasing number of international multi-center clinical trials

205 applications submitted to FDA;132 approved.





Risk consideration on supervision of clinical trials conducted in China

- How to ensure each subjects' rights and welfare well protected and ethical issues well known
- How to avoid or minimize unexpected risks arising from drug R&D
- How to evaluate ethnic differences
- How to ensure safety of healthy subjects
- How to avoid unbalance and unfairness on occupation of medical care resources between clinical trials supported by domestic and overseas sponsors.

Characteristics of supervision of clinical trials in China

◆Written approval must be obtained from SFDA before a new drug clinical trial commences

◆Sites conducted clinical trial must be obtained the certificate of qualification of medical institution conducted clinical trial

◆It is prohibited to conduct the clinical trials of the same investigational drug by the different sponsors at the same time at one site, and the site is not allowed to conduct much more clinical trials at the same time.

◆Ethical committee affiliated to medical institution, no company-operated ethical committees

Existing international cooperation on drug clinical trial

- Cooperation program among China, Japan and Korea

  focus on study of ethnic differences

- Sino-USA GCP inspector training courses（2010.4-）

  28 Chinese GCP inspector s trained by FDA

Expectation

- Establish steady cooperation mechanism with EAM, to jointly enhance the supervision of clinical trials
- Information exchange: GCP inspection results、SAE、data quality standard
- Capacity building：GCP inspector training


Thank You

Clinical Trials in Russia

Evgeny S. Rogov
MD, PhD, JD

Deputy of Head of Clinical Trials Department
Federal Service on Surveillance in
Healthcare and Social Development (*Roszdravnadzor*)

What are the advantages of working with Russia?

- Country population -142.2 million (73% -urban citizens)

- Highly urbanized Healthcare system
- High recruitment & low drop-out rate
- Experienced, GCP trained investigators
- High quality level of data

Expert bodies we deal with in Russia

- Federal State Institution Scientific Center for Expertise of Medical Products
- Council of Ethics at the Ministry of Health and Social Development

What is important to know?

No approval can be granted for:

- clinical trials of medical devices and equipment
- clinical trials without the aim to evaluate the features of the definite medicine
- Vulnerable groups of patients, such as:

- Under-aged patients
- Military Servicemen
- Convicted persons
- Pregnant women

What is important to know?

- Clinical trials can be performed only by research sites included in the official database of MOH
- Only a person (MD) with at least 5 years of professional experience in research area can be a Principal Investigator
- The developer or manufacturer of the medicine is responsible to insure all participants of the CT

  (all study personnel)

Clinical Trial Research Sites

Proposals:

- Strengthened cooperation with EMA
- Information exchange
- Workshops for inspectors
- Concerted actions including joint GCP inspections
- Trainings for Ethics Committees

Perspectives on the Draft Reflection Paper

David A. Lepay, M.D., Ph.D.
Senior Advisor for Clinical Science
U.S. Food and Drug Administration

September 6, 2010

Perspectives -1-

- FDA Strategies: Parallels to EMA/Reflection Paper
  - Prospective dialogue/planning
  - Post-trial vs. real-time jurisdiction
  - Risk-based prioritization
    - Ethical; data quality; applicability of results
  - Learning and Leveraging

Perspectives -2-

- Some particulars
  - Trial design
  - Applicability of results: To population and to standards of medical practice
  - Independent Ethics Committee review, approval, and continuing review
  - Informed consent (freely given; documented)
  - Vulnerable populations
  - Ability to inspect

Perspectives -3-

- Nuances/Footnotes
  - Confidentiality
  - Compensation/Indemnification
  - Supporting Information/Required Descriptions
  - Enforcement Options/Approaches/Standards

Comments and Recommendations

- Overall favorable opinion of the Draft Reflection Paper at U.S. FDA
- Value of "guidance(s) for implementation" and scheduled periodic trending and review of implementation practices
- Stakeholder input/dialogue
  - Especially the impact in nuanced areas where regulation vs. guidance may differ (e.g, E.U./U.S.)
- Stress the need for documentable, verifiable performance

INTERNATIONAL WORKSHOP

DRAFT REFLECTION PAPER ON ETHICAL AND GCP ASPECTS OF CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE CONDUCTED IN THIRD COUNTRIES AND SUBMITTED IN MARKETING AUTHORISATION APPLICATIONS TO THE EMA

6-7 September 2010 – EMA, Canary Wharf, London, UK

Session 2:

Clarify the practical application of ethical standards for clinical trials in the context of EMA activities

Regulatory Authorities Perspectives

Harald Enzmann

CHMP member, BfArM, Germany

WHY do we need this workshop?

- **EU Regulations:** Paragraph 8 of the Preamble of Annex 1 to Directive 2001/83/EC
  - Clinical trials conducted in third countries and used in Marketing Authorisation Applications in the EEA or in applications for a Scientific Opinion under article 58 of the Regulation (EC) No. 726/2004, must be conducted on the basis of principles equivalent to the ethical principles and principles of good clinical practice applied to clinical trials in the EEA.

- **Patients' Need:** Kelley RK and Venook AP, N Engl J Med 2010; 363:596-598, 2010
  - *"... participants in the trial that led to the approval of imatinib for treating gastrointestinal stromal tumor"*
  - *"... patient had a gastric gastrointestinal stromal tumor with hepatic metastases that responded to imatinib in 2001. After the patient's small business failed in 2008, the patient discontinued imatinib.*
    The tumor recurred in 2009 with hematemesis..."

Overview

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA

Table of contents

general consensus expected

more complex issue, dissent between stakeholders possible

Expected Ethical Standards
general consensus expected

- **Information/Consent procedure** (3.2. in reflection paper)
  - individual informed consent is paramount (unless incapable of giving consent)
  - In addition, local customs must be respected and permission from a community leader, a council of elders, etc. may be sought
- **Confidentiality** (3.3. in reflection paper)
  - Confidentiality must be maintained
  - Participants are entitled to know any information collected on his/her health.
  - Participants may choose not to receive information
- **Fair compensation** (3.4. in reflection paper)
  - Participants are entitled to fair compensation for damage as a result of participation in research
  - Waivers are not acceptable
- **Applicability of data to EEA population** (3.8. in reflection paper)
  - Scientific and ethical aspects

Expected Ethical Standards

Local ethics committee and national regulatory authorities oversight

- **National regulatory authorities** (3.1. in reflection paper)
  - Approval by the national regulatory Authority of each country in which the trial is conducted must be provided
  - EU competent Authority will notify the National Regulatory Authority of any serious concerns

- **Local or national ethics committee** (3.1. in reflection paper)
  - Approval by the local or national ethics committee must be provided
  - Ethics committees have to be
    - independent from sponsors and investigators
    - pluralist and multidisciplinary (including lay persons / patients representatives),
    - understanding of the community's customs and traditions

- **Use of additional ethics committees is optional**
  - For concerns that may be different in the EEA and in the countries where the studies are conducted (e.g. appropriate choice of comparators) other appropriate ethics committees may be consulted (only ***in addition*** to local or national committees)

Expected Ethical Standards

more complex issues, dissent between stakeholders possible

- **Placebo and active comparator** (3.6. in reflection paper)
  - Safety and wellbeing of the trials subjects are the most important considerations
  - Standard is EEA-licensed (or equivalent) comparator
  - Uncertain assay sensitivity may justify the use of a placebo arm instead of or in addition to a active comparator
  - Participants at all sites should receive comparable treatment options as trial participants within the EEA.

- **Clinical trials in vulnerable populations** (3.5. in reflection paper)
  - Inclusion of participants from vulnerable populations must be justified by their interest
  - Degree of vulnerability and thus justification may vary (e.g. medical students versus those incapable of giving consent)

Expected Ethical Standards

Access to treatment post trial

(3.7. in reflection paper)

Differences in theory and declarations

Art.33 of Declaration of Helsinki (2008)

*At the conclusion of the study, patients entered into the study **are entitled ... to share any benefits** that result from it, for example, access to interventions identified as beneficial in the study...*

WHO (CIOMS) Guideline 5

*subjects **must be informed, whether**, ... any products ... proven by the research to be safe and effective will be made available to them after they have completed their participation ... and whether they will be expected to pay for them.*

Study participants should benefit from study results

versus

Continued post trial treatment cannot be used to mend the problems of health care systems

Access to treatment post trial

Consensus in reality – stakeholders act responsibly

"…patient had a gastric gastrointestinal stromal tumor with hepatic metastases that responded to imatinib in 2001. After the patient's small business failed in 2008, the patient discontinued imatinib. The tumor recurred in 2009 with hematemesis…"
Kelley RK and Venook AP, N Engl J Med 2010; 363:596-598, 2010

More details from the correspondence with Dr. Kelley and Prof. Venook

- *"The trial these patients were participants in was sponsored by the National Cancer Institute" (post approval commitment, assessment of different doses).*
- *"Novartis's patient assistance program has provided invaluable support to many of our patients with limited financial resources (**including cases from this article**)"*
- *"In our experience, patients are usually unaware that the drug companies have these programs until we talk about it with them and provide contact information."*

Our ultimate goal:
Alignment of all stakeholders in a fair, transparent and predictable procedure

Additional slide

The Way Forward - Proposed Actions

- The reflection paper will provide a consensus position on ethical standards expected in EU marketing applications
- A description of the adherence to these ethical standards should be mandatory for every application.
- Assessment of an application will consider both scientific and ethical aspects.
- GCP inspections may be used to verify the contents of the application.
- EU Competent Authorities will refuse to consider data from studies with Insufficient ethical standards and communicate their concerns to the National Regulatory Authorities who approved the study.
- The assessment of the ethical standards will be included the European Public Assessment Report (EPAR)

European Federation of Pharmaceutical Industries and Associations

EMA International Workshop on Draft Reflection Paper on Ethical and GCP aspects of Clinical Trials in Third Countries

Session 2: Practical Application of Ethical Standards

Sponsor Perspective
Peter Walton
EFPIA/GlaxoSmithKline
EMA – 6 September 2010

General Thoughts

- EFPIA welcomes this important initiative and the publication of the draft reflection paper

- EFPIA supports the major objectives:
  - Development of an appropriate EMA framework for CTs conducted in 3rd countries
  - Clarity and transparency on ethical standards

Section 3.6 Placebo and active Comparator

"*Regardless of location ... the standard of care and comparable treatment options as ... EEA*"

- Standards of care differ, even between wealthy countries with sophisticated healthcare systems, e.g. within EEA, and between EEA and US
- Examples include, first-line medication choices, use of expensive technologies, thresholds for hospitalization
- Concern that will introduce an inappropriate barrier to the conduct of trials in 3rd countries

Section 3.7 Access to Treatment Post Trial

"*The availability of an intervention shown to be successful to the participants in the research once the research is complete ....*"

- Blanket commitment would not suit every scenario, either for provision of study drug, or maintaining standard of 'Clinical Trial care'
  - Company stops the development of the drug
  - Successful submission in a country with a 2-tier healthcare system
  - High frequency of hospital visits during a trial are shown to be beneficial

Section 3.5 Vulnerable Populations

"Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests..."

- Exhaustive list of examples also includes women and economically disadvantaged
  - Better to say anyone in a dependent relationship with the clinical investigator

Section 3.1 Ethics Committee Review

"... regulators support compliance with local requirements ... as well as ... international ethical and good clinical practice standards."

- Many studies involving 3rd countries also have EEA participation:
  - no additional Regulatory & IEC approval steps
- Many studies are performed in 3rd countries with sophisticated regulatory and ethical oversight mechanisms (e.g. US, Canada, Aus):
  - no additional Regulatory & IEC approval steps.
- For a study conducted solely in countries without ICH GCP or WHO standards:
  - the opinion of an EEA Reg Authority IEC would be sought as well as a local one.

Conclusion

- EFPIA welcomes this important initiative and the key principles in the draft reflection paper

- There are, however, a number of practical issues which require clarification and addressing during the consultation period

Raffaella Ravinetto
Institute of Tropical Medicine Prince Leopold, Antwerp

Ethical standards for clinical trials conducted in third countries and submitted in marketing authorization applications to EMA: perspectives of a non-commercial sponsor

Non-commercial clinical trials

- Sponsor: university, hospital, public scientific organization, non profit institution, patients' organization or a researcher
- No participation of the pharmaceutical industry
- No agreements with third parties for regulatory or marketing purposes, not part of development programme for a MA
- Results can orient national or international therapeutic guidelines, and prompt changes to prescription patterns and registration profile
- Product Development Partnerships: commercial and non-commercial entities cooperate to develop a product

(*) EC Draft guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice

The Institute of Tropical Medicine Prince Leopold, Antwerp

Sponsor of post-registration North-South collaborative trials, to:

- address research questions relevant to the study population
- get independent post-registration data to orient guidelines
- empower Southern researchers *(partnership)*

Challenges and constraints:

- Locally: resources, regulatory/ethical systems, vulnerability…
- External funding: poor flexibility to design a research plan

Vulnerable populations

- Vulnerability: diminished capacity of *free* decision-making (autonomy)
- Communities: language, illiteracy, gender, community pressure, hierarchical structures, poverty, *lack of access to health care* …
- *Helsinki Declaration, art.17* "Medical research involving a disadvantaged or vulnerable population or community is only justified:
  - If the research is responsive to the health needs and priorities of this population or community
  - and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research"
- Do the classical protection tools always work?

Ethics committee review

- Ethical principles are universal and non negotiable, while their translation in procedures and practices depends on cultural difference and resource constraints
- Double ethical review for all externally-sponsored trials:
  - complementarity of opinions (partnership modality)
- Regulatory guidance needed for conflicting opinions:
  - to promote proactive dialogue among ECs
- The same principles should apply to regulatory review

Access to treatment post trial

- To be planned in advance
  - Post-trial access to individuals
  - Availability to the study populations
- At population level
  - model of Product Development Partnership (e.g. DNDi)
  - dialogue with national and international health authorities
  - submission for MA in the country
  - “access” plan (e.g. preferential prices, IPR-measures…)

Choice of comparator

- *Helsinki Declaration, art.32*: "… tested against those of the best current proven intervention, except in the following circumstances:
  - …. in studies where no current proven intervention exists; or
  - … is necessary to determine the efficacy or safety of an intervention and the patients … will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option".
- In most cases, a placebo will not be acceptable
- Vulnerable populations: care must be put to avoid exploitation
- Trials outside the EU for MA in the EU: double standards between EU and non-EU countries must be avoided

Clinical trials conducted in third countries

- Relevance to the study population is always mandatory:
  - Responsiveness to local essential health needs and
  - Reasonable likelihood that the population will benefit from results
- Avoidance of North-South double standard practices:
  - Moral, if not legal, obligation
- Translation of universal ethical principles in contextualized procedures, to the benefit of study subjects
- North-South mutual learning and partnership
  - Also among ethical and regulatory bodies

Session 2: Clarify the practical application of ethical standards for clinical trials in the context of EMA activities

Ethics Committee Perspective

Cristina E. Torres

Forum for Ethical Review Committees in Asia and Western Pacific

Key topics

- Ethics committee review
- Choice of comparator – placebo/active comparator
- Clinical trials in vulnerable populations
- Access to treatment post trial

Ethics committee review

- Ethics committee review framework: Enforce international ethical and GCP standards and local requirements
- In countries with limited frameworks for ethical review or regulatory oversight:
  - Submit to an EC that apply equivalent EU standards and *EC to consult with EC members from a country with similar socio cultural background and a local EC*
  - *Support capacity building of ECs in host countries*
- Expertise of reviewers should be documented by the EC.

Clinical trials in vulnerable populations

- Comprehensive definition of vulnerability and types of vulnerable subjects will aid ECs that review the clinical trials.
- *Ethical consideration section of the protocol should make a vulnerability declaration, justify the use of vulnerable subjects, provide corresponding consent forms and define potential benefits of the trial to the individual or society*

Choice of comparator – placebo/active comparator

- *Ethical consideration section of the protocol should define how risks are addressed/ minimized when placebo is used.*
- *Protocol SOPs should clearly define safety measures when placebo comparator is used*
- *Withdrawal criteria should be clearly stated in the protocol.*

Access to post trial benefits

- Subjects should be informed about arrangements to make successful products available to them after completion of the study
- *Ethical consideration section of the protocol should specify how access to post trial treatment is complied with*

Summary of key recommendations

- *Support capacity building of ECs in host countries with limited regulatory and ethical review capabilities.*
- *The Ethical Consideration Section of the protocol should state how ethical issues related to use of placebo comparator, vulnerable subjects and post trial access will be addressed.*

Ethics Committee perspective

Ock-Joo Kim

The Korean Association of Institutional Review Boards (KAIRB), Korea

INTERNATIONAL WORKSHOP: DRAFT REFLECTION PAPER ON ETHICAL AND GCP ASPECTS OF CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE CONDUCTED IN THIRD COUNTRIES AND SUBMITTED IN MARKETING AUTHORISATION APPLICATIONS TO THE EMA

6-7 September 2010 – EMA, Canary Wharf, London, UK

Key issues with which you agree

- *3.6 Placebo and active comparator* "Research shall neither delay nor deprive trial participants of medically necessary preventive, diagnostic or therapeutic procedures".
- "Regardless of the location of the trial, all patients participating in these trials should receive the same or a similar standard of care and comparable treatment options as trial participants within the EEA."
- *3.7 access to treatment post trial* clarification of health care services before the trial in the protocol.

Key issues to be modified

3.7 Access to treatment post trial needs

- it requires only clarification of health care services before the trial.

- "the research protocol describes arrangements for post-study access by study subjects to interventions identified as beneficial in the study or other appropriate care or benefits."

Declaration of Helsinki (2008)

Additional Principles for Medical Research Combined with Medical Care

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

issue to be modified

- Ethical requirements for research in emergency situations (line 360-366) need to be treated distinctively from other research with incompetent subjects in non-emergency condition

– *For persons who are not capable of exercising autonomy … may be undertaken only if the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law and having received adequate information, ….*

Major items to be included and are not in the paper (1)

- Quality Assurance of Ethics Committees. -> “Ethics committees that are truly independent , professionally sound and adequately resourced” [6. International cooperation]

- Establish a collaborative mechanism to ensure quality of ethics committees in the third world.

- Clear guidelines on the role of a local ethics committee for of the international studies that involves many centres.
- Avoid unnecessary duplication of review of the same protocol, especially scientific review of the protocol.

Major items to be included and are not in the paper (2)

- Monitoring of risk during the trial by ethics committee
  - must do; can do; may do; be desirable to do
  - Clearer role division between sponsors, ethics committees, and regulators

- Clearer guidelines for the ethics committee for acceptability of placebo trials and washout

- Need for ‘an impartial witness” for wider category
  - consent process not only for illiterate population, but also for other situations such as trials with vulnerable population

Summary slide

Key recommendations for the finalization of the paper and for the future

- Clarification and highlights of regulatory action/ action plan for each ethical standard - a power to enforce it.

- Inclusion of national & international efforts for ensuring quality assurance of ethics committees.
- Clarification of roles of ethics committees in monitoring clinical trials including review of adverse drug reaction.

- Specification of shared responsibility among ethics committee, sponsors and regulators for monitoring of the trial.

- Requirements for access to treatment post-trial need to be more than clarification of the plan.

GEISER Fundación

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

International Workshop on Draft Reflection Paper On Ethical And GCP Aspects Of Clinical Trials Of Medicinal Products For Human Use Conducted In Third Countries And Submitted In Marketing Authorisation Applications To The EMA

UNDERSTANDING VULNERABILITY IN LA&C
– focus in rare diseases -

Virginia A. LLera, MD
www.icord.se
www.fundaciongeiser.org

EMA, London, September 6-7, 2010

Do “vulnerabilities” has the same meaning all over the world?

Streets with no name at LONDON CITY (pop. 2,134), Catamarca, Argentina.

I. Clinical Trials in vulnerable population

- **Vulnerability** :

This concept emerge as a result of the relation between the patient / environment /Cultural Context ,and also including the impact of the specific disease.

- The information is not an isolated act , it is a mental process and, as a process includes steps , time, etc.
- The information process needs to be design accordingly to the specific vulnerability .
- The information consent is only one of the steps .

I. Vulnerability and information

Frame	Prevalent Condition with risks	Neglected Diseases	Rare Diseases	**Action plan**
Regional	Official info available	Info not accessible	None or poor info	Availability of info at official spaces.
Family	Accessibility to support procedures	No steady support programs	No type of official support available.	Gov, NGO and sponsors coordination of educational programs
Personal	Not always active. Losses are already considered.	Scarcely pro-active	Interest and need of participation, but with orientation.	Visible EC for patients and with capacity to inform.
Inter-national (i.e. WHO/ PAHO)	Info and guides worked-out at WHO	WHO clearly invest but there is no NGO participation.	Lack of knowledge and priority at WHO	Recognition of vulnerabilities, classification and adoption of measures

II. Ethical Committees (EC) reviewed

Are all the EC the same?

Both are red cars, but different…

- Culture: LA&C countries does not have a culture focussed on the citizen.
- Official info: do not satisfy population needs, and the access is difficult for many.
- Gov control: poor/disorganised
- Composition of EC: mainly formal. Patients do not participate with decision.

II. Ethical Committees (EC) reviewed

- EC role: formal regulator of rights vs. connector of regulation and communication.
- i.e., EC should meet patients under recruitment, explain the available alternatives in information and how to access to official info sites. (breaking the info dependence with the research team)
- Congruently, the regulatory authorities should publish info related to the on-going clinical trials in the country by means easily accessible.
- International harmonization for EC members.

III. Access to treatment post trial

Is there any sense to do an effort to be part of a CT and have no possibility to enjoy the benefits ?

- The **core** of the research is the welfare of patient .
- Patient decide to be part of CT because they want to live more , to live better. They do an effort because they want to live as a healthy people .
- There is also more especial situations :
- A) When the CT brings the only treatment available for a disease
- B) When the participation of the 3th world is vital (rare diseases , Neglected)

VI. Choice of comparator – placebo/active comparator

- Local reality may be different. Due to previous lack of patents active alternatives may be available in the region.

Conclusions

I. Vulnerability:

- A better understanding of its nature in LA&C.
- Consider its link to information
- Consider its identification and special measures for each type.

II. Ethical Committees:

- Should be adapted to regional vulnerabilities
- Consider its appropriate composition
- Consider its compromise with the patient needs.

III. Access to treatments:

- Besides affordability, access should consider the options in the market, and when there is no option a balanced policy should be intended.

IV. Election of comparator:

- Priority of local reality should be given.
- Reinforce protective measures according to the detected vulnerabilities.

Understanding some other the local needs in LA&C

- Diseases may have the same origin. But time to diagnosis, interactions with foods and local medicines, access to therapies, co-morbidities, and many other factors differs, then the outcome may differ. A separate regional analysis of data is always needed.

- Accessibility to medicines is more difficult in the region. A differential policy is needed. Economical approaches should be balanced.

- Many research procedures are formally undertaken. But there is still a way to reach a good practice, a culture of cooperation, a spirit of devoting to patients, and a deep understanding of why are clinical trials developed in the region should be worked out together with the introduction of technologies and financial support for investigations.

To take home

- In many circumstances LA&C can be an optional region to expedite EU research and make it more affordable, but being involved with rare diseases, LA&C would be each time more and more demanded.

- Rare conditions are politically, socially and economically out of the main conflicts of interest in the region. A good opportunity to start harmonizing with EU needs.

Ethical Considerations for Clinical Trials in the Context of Patient Centered Care

Patient Perspectives

Perry D Cohen PhD
Parkinson Pipeline Project

6 Sep 2010

Benefits from EMA Leadership

- Establish a framework and process for international discussion of fundamental ethical constraints as a basis for greater cooperation on standards for clinical research
- Engage and incorporate patient perspectives, as the essential viewpoint on questions of valuation of the risk-benefit tradeoffs
  - Build patient trust, faster, better recruitment,
  - Gain therapeutic insight from collaboration
  - Patients gain from participating and from outcomes

Overview of Ethical Issues

- Appraisal of ethical standards
  - Comprehensive - cover major issues of interest to patients
  - patient protections beyond those found in the USA
- Major concerns:
  - Need to protect patient interests without being a barrier
  - Need for intermediate sanctions for violation of standards without stopping studies which harms patients
- Roles for patient advocacy organizations and well qualified patient as
  - consultants to sponsors and regulators on patient perspectives
  - trusted stewards to protect the privacy of patient data and guide the appropriate use of aggregated databases from interoperable data exchange standards for electronic medical records

Appraisal of Ethical Standards Specific Comments

- Choice of comparator – placebo/active comparator– sham brain surgery
- Access to treatment post trial—business decisions
- Clinical trials in vulnerable populations
- Ethics committee review - Institutional Review Board (protection of human research subjects)
  - Informed consent – Research Participants Bill of Rights and Responsibilities (www.pdpipeline.org)
  - Confidentiality

Choice of comparator – placebo/active comparator

- Aligned interests
  - Rigorous research design
    - Randomized controlled trials, equipoise
    - Blinded outcome assessment
  - Research needed on placebo response (strength, length), effects of blinding, etc.
- Divergent Views
  - Minimize false positives (experimental model) vs. minimize false negatives (patient view)
  - Control group: sham brain surgery (US neurologists) vs. best medical/surgical treatment (patient view)

Access to treatment post trial

- Aligned interests -- Continuity of treatment
  - patient interests in continuity of helpful therapy
  - sponsors interest in building a cohort of users to purchase the product once it is on the market
- Discontinuity – proprietary business decisions
  - Intellectual property/patent life -- market exclusivity
  - Proprietary business practices undermine trust
    - No legal relationship between sponsor and experimental volunteer.
    - Cite patient interests for non-transparent business decisions.
  - Example: Amgen and GDNF

Vulnerable populations

Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research". Pg.17

- Vulnerable US populations:
  - Persons who have serious, potentially disabling or life-threatening diseases
  - volunteer for clinical trials based on the expectation of benefits

Standards for protection

- Good Clinical practice standards - EU
  - "The rights, safety, and well being of the trials subjects are the most important consideration and should prevail over the interests of science and society." pg.7

VERSUS

- "Therapeutic misconception" USA
  - Counsel subjects that in clinical research, patients should not expect personal benefit, the needs of the research come first

Ethics Committee

"It is an important element of international cooperation that regulators support compliance with local requirements in each country as well as reinforcing international ethical and good clinical practice standards." (pg.8)

- Local ethics committee – Institutional Review Board (IRB) – independent, have right to monitor, authority to prohibit study
- Transparency of processes, disclosure of conflicts of Interest
- Provisions for vulnerable populations
- Consider centralized, disease based IRB- to take into account and build knowledge about clinical trials.

Confidentiality - Privacy

"To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular international human rights law".

- A call for privacy protection rules indicate lack of trust
- Patients will give up some privacy to advance the science
- Privacy protection is an ongoing process of building confidence
  - Stewardship role as gate keeper for trusted patient advocacy organizations to address public concerns
  - Interoperable data exchange standards and aggregation of large data bases for research and quality management depend on flexible standards and easy access to data

Session 2: Clarification of the practical application of Ethical Standards for Clinical Trials on medicinal products for human use in the context of the EMA activities

Patient Perspective

Hawa Dramé – FITIMA

Burkina Faso/Guinee

London - 06 Sept 2010

Key Issues with which I agree

3.1: ***Local Ethics Committee and National Regulatory Authority***

- Setting up local independent ***Ethics Committees***
- Participation of ***Patient's representative***
- Usefulness of a « ***Cultural Mediator*** »

3.2 : ***Information / Consent Procedure***

- Written consent, signed and dated by subjects involved in the Clinical Trials

Key Issues with which I agree

3.3 : ***Confidentiality***

- Respect of patient confidentiality - Especially when doing genetic tests or tests involving children

3.4 : ***Compensation***

- Fair compensation for damages or injuries

3.5 : ***Population***

- Particular attention should be given to vulnerable or dependant patients

Key Issues with which I agree

3.7 : ***Access to treatment post trial***

- The research is responsive to the health needs and the priorities of the population or community

Issues identified in some countries

- There are no « **Ethics Committees** » in several countries or only theoretically
- ***Protocols*** *are rarely or not submitted to the EC*
- *Failure to obtain* ***written consent***
- *Lack of* ***GCP Training***
- Lack of **information** about the study for the subjects involved in the trial

Major items should be included

3.1 : Local "Ethics Committee"

- Support in setting up « Ethics Committees »
- Harmonise the « Ethical requirements »
- *Additional training and capacity building for Healthcare Professionals and members of « Ethics Committees » - « EDCTP »*
- Introduce « Ethical requirements for clinical research » in Universities and training programmes
- Controls / Audits, monitoring of the studies

Major items should be included

3.2 : Information / Consent Procedure

- Process adapted and Consent form Specific for vulnerable or susceptible trial subject: risk/benefit

3.5 : Vulnerable populations

- To give the priority to the protocols including studies on « Neglected Diseases »

Major items should be included

3.7 : Access to treatment post trial

- Medicinal products should be made available to Clinical Trials' subjects despite the cost and the duration of treatment

- Encourage a « specific » policy on negociated prices for host countries with low incomes

KEY RECOMMANDATIONS

- **Support** the setting up of « **Ethics Committees** »
- **Harmonise** the « Ethical codes » (ICH/GCP)
- Training and **capacity building** for Healthcare Professionals and members of « Ethics Committees »
- Controls / Audits, **monitoring** of the studies
- Establish **Specific Process** of « Informed Consent » for subjects unable to read or to write
- Encourage studies on «**Neglected Diseases**»
- Provide **access** to medicinal products after Clinical Trials
- **Prices** of the medicinal products should be related to the country's standard of living.

Session 3

ANVISA
National Health Surveillance Agency
Brazil
Clarice.petramale@anvisa.gov.br

Agência Nacional de Vigilância Sanitária
www.anvisa.gov.br

Clinical Research in Brazil

- Over 300 new studies/year
- 80% multinational, phase III research
- Focus in new drugs applied to cancer, HIV, diabetes, cardiovascular diseases
- Vaccines
- Medical devices: cardiac stents
- Performed mainly in public sites, located in university hospitals

Anvisa's concerning in respect to ethical issues

- The compensation by insurance or indemnity, really, does not occur
- SAEs are often sent to the public health system consuming public resources
- The inclusion of vulnerable populations, elderly and/or poor educated people occurs frequently and without an appropriated plan of communication
- In some cases bio banked samples can have poor justification
- The access to treatment post trial may be uncertain
- Swift over study medication to regular treatment may be traumatic.

Anvisa's concerning in respect to technical issues

- The import process of products and samples
- GCP in transporting and storing
- Requirements for a proper research budget
- An appropriate monitoring process
- SAEs monitoring: signals of alert
- Validation of trials data for registration (MAA)
- Research not applied to the needs of the country

Suggestions for NRAs

- NRAs must act as a global network
  - Sharing private information in SAEs Systems that can raise regulatory alerts.
  - Sharing information about research budget; ethical problems or problems with the protocol and the measures NRA adopted to fix them.
- Develop activities in company like inspections, workshops and meetings to discuss new regulation
- Develop strategies to motivate industries to consider the health needs of the populations in their plans of new drugs.

Thanks for your attention

www.anvisa.gov.br

International workshop:

DRAFT REFLECTION PAPER ON ETHICAL AND GCP ASPECTS OF CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE CONDUCTED IN THIRD COUNTRIES AND SUBMITTED IN MARKETING AUTHORISATION APPLICATIONS TO THE EMA

Session 3:

Determine the practical steps to be undertaken during the provision of guidance and advice in the drug development phase

Dr Detlef Niese

EuropaBio / Novartis Pharma

General comments

- EuropaBio welcomes the EMA Reflection Paper. In general, we find it is well aligned with EuropaBio's core ethical values and addresses important issues related to the conduct of clinical trials in a globalised world

- The practical steps suggested by the document are very relevant and part of the routine development planning and conduct by EuropaBio member companies

General comments cntd

- EuropaBio agrees that a sponsor should not conduct clinical trials in any country outside the EEA if it is not ethically acceptable to conduct the trial within the EEA
- However, given the diversity of opinions within the EU member states sponsors would welcome more clarity on
  - Which ethics committee EMA expects to provide the necessary opinion
  - How a sponsor is expected to deal with different views by multiple ethics committees
- It would be also be helpful to understand how the agency plans to assess ethical standards and regulatory risks in countries outside the EEA and how they plan to communicate the results of this assessment

Assessment of Therapeutic Needs in the EEA

- Applicability of selected indication to the EEA population -

- Proposals are in principle reasonable
- In general, clinical trials are conducted in countries where the sponsor plans to seek approval to market the product
- For the assessment of extrinsic factors (ethnical diversity, living conditions) reference should be made to the ICH E5 guideline
- Third country trials may investigate diseases prevalent outside of the EEA and those prevalent wihtin EEA countries

Feasibility of Clinical Trials

- Sponsors are used to assess the feasibility of every clinical trial before its implementation
- Sponsors would like to better understand the relevance of the feasibility assessment for the regulator:
  - Why would the regulator need to have the recruitment plans and timelines?
  - What is the value of submitting selection criteria (every trial protocol includes the planned centers and countries)?

Assurance of Data Quality

- EuropaBio agrees that the measures proposed in this section are critical to assure the quality of any clinical trials
- However, they are not specific to third country trials and also relevant to trials conducted within the EEA countries e.g.
  - Complexity of trial design based on the trial objective and endpoints
  - Access to comparator, diagnostic procedure, formulation etc required by the protocol
  - Quality of data monitoring and training of investigators
  - Diverse ethnicities
  - The study design must always match the requirements of the population where the trial runs
  - Identification of standards of care

Assessment of *Potential Weaknesses* of the Regulatory or Ethical Review Framework

- The reflection paper requires an assessment of the quality of the regulatory and ethical review framework for any country where clinical research is to be conducted
- While EuropaBio agrees with the need of such an assessment results are likely to be subjective and variable
- It would be helpful to understand which criteria and standards the EMA expects to apply for such assessment e.g.
  - Structure, legal basis and competencies of local regulatory authorities
  - Independence, training and accreditation of ethics committees
  - Implementation of standard SOPs
  - Legally binding implementation of GCP
  - Accepted references for GCP and ethical standards

Regulatory Action Planning

- Scientific Advice is an appropriate and welcome tool to understand & improve the likelihood of success of any clinical development plan

However

- More transparency would be welcome as to which ethical standards the agency considers acceptable (aside of the EU directives and guidelines)

- Defined mechanisms are needed for assessing the quality of ethics committees and the regulatory system in third countries

- While it is understood that Scientific Advice is non-binding on regulatory authorities, sponsors and not the least research participants would benefit from assurance that final regulatory action would consider the original advice given

Session 3: Practical Steps to be Undertaken During the Provision of Guidance and Advices in the Drug Development Phase

Elizabeth Madichie, Ph.D.
Association of Clinical Research Organizations (ACRO)
Pharmaceutical Product Development, Inc.

6 September 2010
EMA International Workshop: Third Country Trials

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Advantages of Multi-Regional Clinical Trials

- Availability of patients shortens recruitment time (numbers, numbers, numbers)
- Availability of investigators and site personnel
- Broad adoption of GCP allows consistency
- Research quality standards are consistent worldwide – proof of compliance is required by regulators in every major market
- New markets (safety and efficacy demonstrated for multiple regulators)

The Case for Globalization: Ethical and Business Considerations in Clinical Research. Clark, Voice of Insight Consulting, July 2009

To view the full report, please visit:
http://www.acrohealth.org/globalization-white-paper.html

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Therapeutic Needs

- Principles to assure therapeutic applicability to the European population as proposed are an established step in the drug development plan
- As part of the commercial assessment, evidence is accrued relating to the likely countries for the study - these are based on medical need and that drives both recruitment and commercial opportunity
- Limitations of data extrapolation from non-EU to EEA patients are fundamental considerations

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Feasibility of Clinical Trials

- Principles of feasibility assessment focus primarily on ability to conduct the trial in accordance with protocol
- Protocol is designed to reflect the objectives of the development plan, future licensing and commercialization objectives
- Indirectly, product development plans do address this section of the reflection paper

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Data Quality

- Consistent standards are applied regardless of the location of the trial
- Third countries can be more stringent than developed countries
  - placebo rational for Latin America
  - conduct of early phase trials in India
  - level of documents requirements in China and Korea
- Third countries should not be regarded as developing countries

Scientific Advice

- Need to ensure advice and guidelines enable evolution of clinical practice and innovation
- Global commercialisation needs drives consistency of approach to product development, divergence could be counter-productive
- Concerns over suggestion to require scientific advice in advance of commencement of trials including third countries
- EU intrinsic population differences may be as large as extrinsic populations

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ACRO Recommendations

- Further refinement of definition of “third country.”
- Risk assessment measures to evaluate difference in data gathered from non-EU patient and EU patients.
- Recognition of the role of third countries in advancement of clinical research, drug development and human health.
- Support the adherence to ICH GCP by all researchers globally.

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EMA reflection paper on Ethical & GCP aspects of CT 3rd Countries – EFGCP comments

Dr. Colin Wilsher

Pfizer Medical Quality Assurance

What is the European Forum for Good Clinical Practice (EFGCP)?

A non-profit organisation established by and for individuals with a professional involvement in the conduct of biomedical research.

Ensuring good data quality when conducting trials

- Concern that guidance should not restrict access to or availability of, Clinical Trials in 3rd Countries because of more stringent requirements than those required in the EEA.
- Care should be taken that maximal proposals are not accumulated in an additive fashion such that 3rd Counties are actually disadvantaged compared to EEA. Additional requirements should be examined to see if they do offer improved ethical coverage.

Example of additional requirement

Line 315 "National or local ethics committee ….. ***When uneducated or illiterate persons form the focus of a study they should also be considered for membership or invited to be represented and have their views expressed"***

Proposed change: "When uneducated or illiterate persons form the focus of a study they should have their views expressed to the committee".

Comment: It will be extremely difficult, if not impossible, to have uneducated or illiterate persons become a member of the ethics committee. Properly constituted Ethics Committee should already consists of members who's remit is to express the views on behalf of various patent groups.

Clarification needed

Line 307

"When the sponsor is an international organisation, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards and the research protocol should be submitted for ethical and scientific review in the country of the sponsoring organisation and the ethical standards applied should be no less stringent than they would be for research carried out in that country."

What is meant by "international organization" (pharmaceutical company? Non-profit foundation? Patient organization? WHO? If they are "international" what is the country of the organisation?

Proposed change: "When the sponsor is an organisation based outside of the country where the study is performed, the ethical standards applied should be no less stringent than they would be for research originating in other countries where it operates."

Consent renewal

Line 358

"The informed consent of each subject shall be renewed if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate, **and in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research**.

Proposed change: "The informed consent of each subject shall be renewed if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate and in long-term studies investigators should be diligent in ensuring that subjects maintain their consent."

Comment: The simple act of re-signing of a consent form does not in itself provide any additional safeguards in ensuring the subject maintains effective consent. The process of consent is a continuing one (not just a one time signing of a consent form) and requires investigators to continually ensure that subjects are fully informed and fully maintain their consent to continue.

Vulnerable populations

3.5. Vulnerable populations Example of vulnerable subjects are patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, homeless persons, nomads, refugees, prisoners, minor and those incapable of giving consent. Other groups or classes may also be considered vulnerable (**e.g.** elderly persons, **people receiving welfare benefits or social assistance** some ethnic and racial minority groups **and individuals who are politically powerless**). "*Vulnerable subjects include "members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention*". "*Persons who have serious, potentially disabling or life-threatening diseases are highly vulnerable*".

Comment: This section extends the definition of vulnerable subject to include those "incurable diseases", "persons in nursing homes", " politically powerless" & anyone receiving "welfare benefits". It is important that all subjects be respected however this increases the burden on the researcher to check all these categories and that check does not ensure that there is beter protection.

Vulnerable patients

- Line 1064
- 2.1. Inclusion of vulnerable patients, e.g. children, women, unconscious patients
- “women” are not vulnerable patients

Placebo and active comparator

- 3.6 Placebo and active comparator
- Line 657 requires all patients worldwide to have a similar standard of care and comparable treatment to participants in the EEA. Some studies have a background of "standard of care" which varies across the globe. This may not be possible to standardise as standard techniques and therapies vary from country to country (both inside & outside EEA) and from investigator to investigator.
- Study design & statistical methods control for this variability as it is impossible to standardise

Availability of an intervention

Line 679

- **“**The availability of an intervention shown to be successful to the participants in the research once the research is complete is a question that researchers, sponsors ethics committees, and regulatory Authorities/Governments have to consider in research related to healthcare concerns.”

- **Proposed change: “**The availability of an intervention shown to be successful to the participants in the research once the research is complete and a marketing submission made, is a question that researchers, sponsors ethics committees, and regulatory Authorities/Governments have to consider in research related to healthcare concerns.”

EMA reflection paper on Ethical & GCP aspects of CT 3rd Countries – EFGCP comments

www.efgcp.eu - info@efgcp.eu

Federal **A**gency for **M**edicines and **H**ealth **P**roducts
(FAMHP)

Determine the practical steps to be undertaken during the Marketing Authorization phase.

Regulatory Authorities perspective

Pieter Neels
CHMP member

06/09/2010

Introduction

Legal Bases for the present discussion paper:

- Directive 2001/83/EC
  - Paragraph §8 of the Preamble – Introduction and General Principles of Annex 1
  - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF
- Regulation (EC) No EC/726/2004
  - Recital 16
  - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:En:PDF

Recital 16

There is also a need to provide for the **ethical** requirements of Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (1) to apply to medicinal products authorised by the Community. In particular, with respect to clinical trials **conducted outside the Community** on medicinal products destined to be authorised within the Community, at **the time of the evaluation of the application for authorisation**, it should be verified that these trials were conducted **in accordance with the principles of good clinical practice and the ethical requirements** equivalent to the provisions of the said Directive.

Article 56 (4)

The Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use may, **if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.**

As a consequence, the Marketing Authorisation **evaluation** should ensure that these GCP principles have been applied to **all** submitted clinical trials, and, that **ethical guidance is sought if required**.

Points to consider during evaluation

This relates to the concern over the design of studies in relation to acceptability in Europe.

- to the use of placebo or
- duration of use of placebo,
- poorly optimised background therapy,
- use of inappropriate comparator,
- inappropriate investigations,
- lack of consent etc.

Many of these issues include ethical concerns.

Review procedures

- Information should be provided on where each clinical trial was performed and on how ethical requirements were met
- assessors should look for ethical concerns relating to the studies in the dossier to support the MAA
  - ⇒ EC/NCA approval of the CT
  - ⇒ Conduct of the trial
  - ⇒ Vulnerable patients
  - ⇒ Trials conducted in low to middle income countries
  - ⇒ Whether or no EEA EC has reviewed and approved the study/studies for trials performed outside the EU

EU Assessment Report should reflect

1. That steps have been taken to determine that all clinical trials were conducted GCP and ethical requirements
2. The ethical concerns, if any.
3. How these ethical concerns have been solved and whether they had an impact on the assessment of the quality, safety and efficacy of the product,
4. Whether the CHMP has sought additional ethical expertise,
5. The reasons for and outcome of any GCP inspections requested (these may be routine or triggered),
6. Discussion of applicability of data to the EEA population

Actions in case of ethical concerns

1. further clarification from the applicant should be given if unethical conduct is suspected
2. CHMP should develop expertise in ethics who could advise on these aspects as appropriate.
   - A SAG structure similar to a might be envisaged.

Consequences of an unethical study (1)

1. If, (after taking appropriate advice if necessary), the CHMP concludes that a study has not been carried out in accordance with the appropriate ethical requirements then the CHMP must conclude upon additional steps. No single solution will be applicable to all situations, and issues are likely to be complex.

Consequences of an unethical study (2)

2. Therefore the European Medicines Agency /CHMP must have a number of possible tools at its disposal. These may include the following:

   2.1 Assessment of the application without data from the studies or part of the studies deemed unethical. Additional analyses may be required. This may result in an application that is not approvable.

   2.2. The possibility to making public the circumstances and details of studies which were found not to have been conducted in accordance with ethical requirements.

   2.3. A graded system of potential actions should be developed (see 5.3).

Regulatory action/action plan (1)

1. Establishment of a pool of experts to advise CHMP on ethical aspects
   - ⇒ and define their membership,
   - ⇒ required expertise,
   - ⇒ mandate and procedures,
   - ⇒ the process for consultation for CHMP, EMA or other agency scientific committee,
   - ⇒ Such consultation may be on general matters of principle involved in establishing requirements and guidance, or specific cases involving particular trials and products.

Regulatory action/action plan (2)

2. EU Competent Authorities should develop a system for review of MAA dossiers, and identification of studies of potential ethical or GCP concern, involving review at the time of validation by the EMA product team, and during the assessment by the assessment team and CHMP, supported by the EMA product team.

Inspections & Triggers (1)

- GCP inspection is an important tool for monitoring compliance with requirements
- A programme of routine inspections is required
  - ⇒ the possibility for communication and exchange of information with the regulators in the countries concerned
- several criteria may act as triggers for a GCP inspection.
  - ⇒ Some are study-related aspects
  - ⇒ Others relate to the third country issue

Inspections & Triggers (2)

Regulatory action/action plan

1. The criteria used as the basis for both routine and triggered GCP inspections should be further developed.
2. The processes for identifying triggers for GCP inspections should be further developed and systematised.
3. Frameworks for contact with National Regulatory Authorities, to gain information on the GCP compliance and local inspection, in the countries where clinical trials take place should be developed.

Actions in response to non-compliance

Regulatory action/action plan

1. EU Competent Authorities should develop a system for regulatory action in case of non compliance with ethical and GCP requirements.
2. Where clear serious concerns are identify the EU competent Authority should communicate these concerns to the National Regulatory Authority of the Country (ies) concerned.

Thank you for your attention!!!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GCP review & Transparency

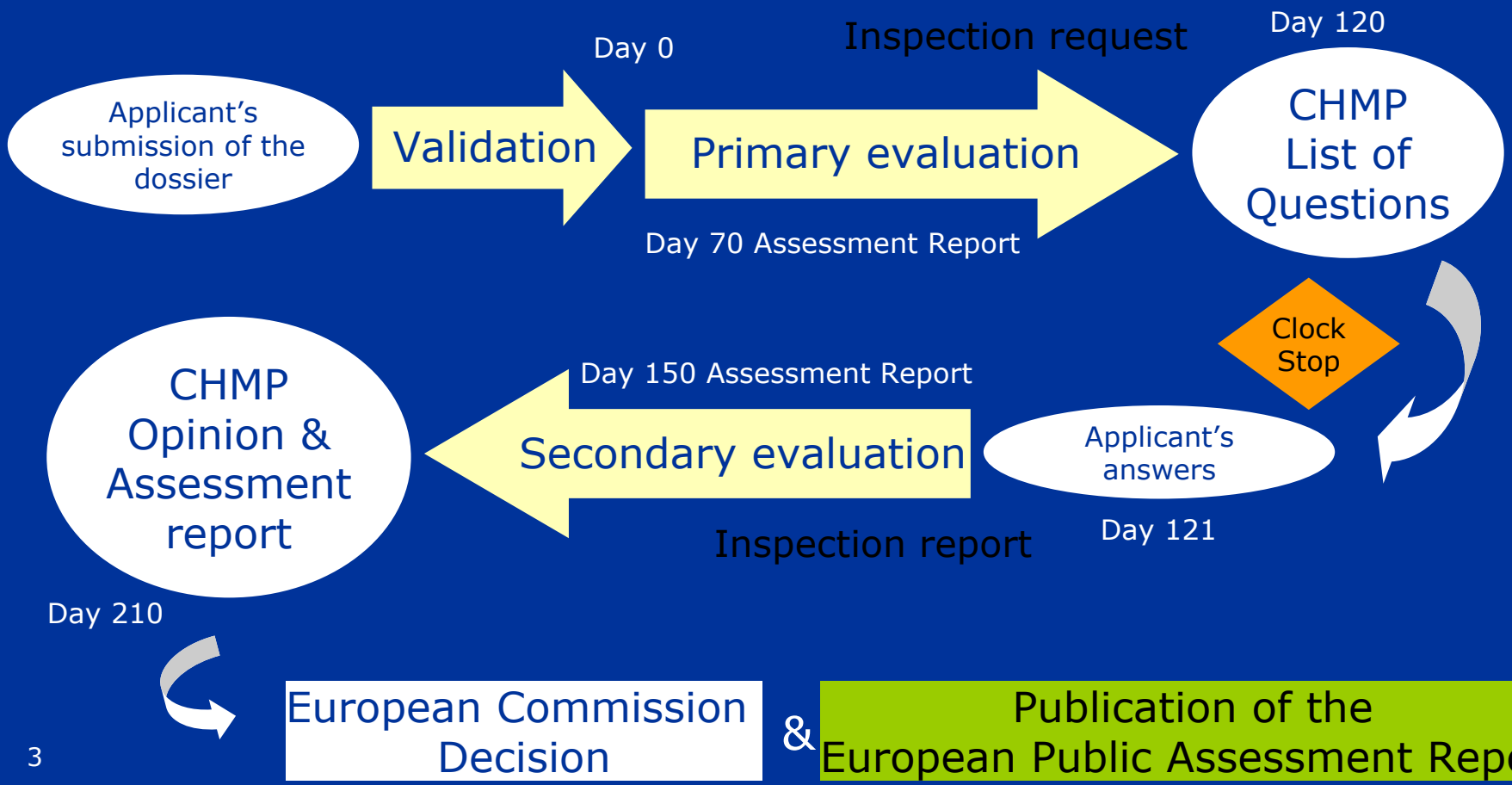
INTERNATIONAL GCP WORKSHOP
6-7 September 2010 – EMA, Canary Wharf, London, UK

Dr Laurent BRASSART
EMA - Medical Information – Information compliance and consistency

Transparency on GCP review: why?

- Patients' right to information about medicines and their development
- To help ensuring the ethical and scientific quality of clinical trials and therefore their validity
- High standards of transparency are part of the legitimacy of any modern administration
- Public trust in clinical trials is an important factor in supporting patients' willingness to participate in trials and their trust in medicines

Evaluation of applications for European marketing authorisations for human medicines (EMA centralised procedure)



Today's GCP information in European Public Assessment Report

- General comments on compliance with GCP and need for inspection
- Information whether the applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC, where applicable.
- Design and conduct of studies; including comparator, major amendments made to the protocol, protocol compliance and reasons for protocol violations.
- Triggers for GCP inspection
- Benefit risk assessment to address potential uncertainties stemming from GCP

Transparency of GCP review in public assessment report

Need for more consistency

- To inform on the steps taken to confirm the application of GCP and ethical requirements.
- More information on where clinical trials took place (± applicability of data to the EEA population)
- Presentation of GCP issue, including inspection outcomes
- Explanation on how deficiencies have been addressed and their consequences

Proposed Regulatory action/action plan (1/2)

The CHMP assessment report and the European Public Assessment Report should describe clearly the clinical trials included in the Marketing Application dossier, listing the trials and details concerning their conduct.

Listing of GCP data of trials submitted

NEW

- Protocol identification and title, dates, sponsor;
- countries & numbers of participants in each country;
- nature of the population (age, gender, vulnerability);
- standards to which the trials were conducted.

Based on Electronic tabular listings provided by applicant

Proposed Regulatory action/action plan (2/2)

The EPAR should describe the assessment of the ethical issues and GCP compliance, the steps (including inspection) taken to confirm this and expert advice sought.

- Any relevant ethical issue should be highlighted as part of the assessment of the individual trial.
  (access to treatment post trial, use of placebo or treatment interruptions, choice of active comparators, treatment of vulnerable populations and applicability of data to EEA population)
- If GCP inspection: reason + outcome + consequences
- When GCP/ethical concerns have been raised:
  - Presentation of the issue,
  - Describe any external expertise sought and the advice received,
  - Discussion and explanation on how deficiencies have been addressed
  - Consequences on the MAA.
- "No ethical issues were identified" may be sufficient where applicable

EMA International Workshop

Draft Reflection Paper on Ethical and GCP Aspects of Clinical Trials of Medical Products for Human Use Conducted in Third Countries and submitted in Marketing Applications to the EMA

Session 4: Practical Steps

Sponsor Perspective

Torkil Fredborg - for the European Federation of Pharmaceutical Industries and Associations (EFPIA)

6 September 2010

What are Sponsors already doing?

- Follow own ethical frameworks to assure that clinical trials conform to the Declaration of Helsinki and other international guidelines.
- Making medicines available as appropriate in countries that contribute to their development
- Design and conduct studies and writing study reports in line with ICH E6 and E3
- Ensure and declare that clinical trials in third countries meet the ethical requirements of Directive 2001/20/EC
- Provide a listing of all trials and third countries involved in Module 1
- Provide specific trial information including the countries involved and the number or investigators and patients per country in the clinical study reports
- Facilitate and assist regulators in their inspections of clinical sites

Ethical Framework* at Eli Lilly

Provides all employees with principles and tools to evaluate the ethics of developing, conducting, analysing and disclosing biomedical studies

Includes the duty to:

- Ensure that biomedical research has anticipated scientific and social value and will benefit people's health and well-being
- Select communities in which the research is done so that burdens and benefits are distributed equitably
- Conduct research that offer benefits to individual research subjects and/or the community and to minimise risks to the extent possible
- Have biomedical research reviewed by one or more independent ethics review committees prior to subject enrolment
- Obtain informed consent of prospective subjects prior to conducting a clinical trial
- Ensure that any product/intervention developed or knowledge generated as a result of biomedical research must be made reasonably available for the benefit of the subjects, population or community in which the research was conducted

***Ref.: Eli Lilly Bioethics Framework for Human Biomedical Research, 2010**

Information to be included in the dossier

- The Directive is clear and Sponsors are already required to declare that studies meet EU GCP requirements
  - In order to do this, companies are carrying out extensive audits internally as well as at investigative sites
  - Eli Lilly applies the same standards to biomedical research, regardless of where the research is carried out

- Appropriate for CHMP to assess ethical aspects, but it should be a focused effort aimed at studies of concern
  - Listing of studies conducted in third countries are already detailed in Module 1.9
  - Detailed information to facilitate assessment of ethical aspects is provided as standard in the individual study reports in Module 5

Validation and assessment issues and process

- Agree that where there is doubt about ethical issues (for third country studies) the CHMP may consult with experts or trigger inspection
  - Need to ensure that such experts have practical experience with clinical trials and global requirements.
- Ethical principles should only be discussed with the applicant when legitimate concerns are raised.
  - This should not detract from the scientific discussions unless significant ethical issues raises questions about the validity of the data presented.
- Agree with international guidelines that clinical research should benefit the community in which it was conducted.
  - EMA/CHMP has no means to enforce this
  - Since the Applicant and CHMP will not be able to reach any meaningful conclusions about the future launch of products outside the EU, it would be unhelpful for an assessor to question this at a time where there are important scientific discussions about the product in Europe

Transparency

- Do not agree that an additional new Annex with summary of all clinical trials substantially improves the assessment reports and hence the EPAR
  - Current application format already guides the assessor to studies in third countries (Module 1.9), which enables in-depth evaluation of the relevant study reports.
  - Regulators should be able to utilise information already provided in dossiers rather than creating new listings
  - EPAR should be readable and focus on issues with the application
- Agree that GCP findings be made public in the EPAR, but need to ensure balanced discussions so as to not erode the public perception of Sponsors and Regulators

"No ethical issues were identified"

vs.

"Studies were in line with current ethical standards"

Conclusions

- Agree with much of the content in the reflection paper, but concerned that it does not take into account what is already covered by global regulations and guidelines as well as company codes of conduct
- Request for additional new Annex to AR – based on information provided by the applicant – should be removed from the paper as assessment should focus on studies of concern

- The draft paper is long and unfocused and risks losing the reader. Some streamlining is needed, particularly emphasizing that regulators need to apply discretion as suggested in line 998
  - It deals only superficially with the fact that ethical concerns may need to be weighed against scientific achievements. Regulators will need to apply judgment in balancing the need for a new treatment with concerns about research conduct
  - Need to recognise that some regulatory requirements can be in conflict with ethical standards. E.g. EMA still requires highest standards of evidence for efficacy against placebo, whereas such studies are not allowed by European Ethics Committees.

Making Medicines Affordable

EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

Standpoints/Comments of the European Generic Medicines Association on the Practical Steps Regarding Ethical and GCP Aspects in the Draft Reflection Paper EMA/712397/2009

London, UK, September 6, 2010

Pavel Farkas

Bioequivalence Working Group, EGA

Biopharmaceutics, R&D Teva Generics System

EGA standpoints and key issues

- EGA welcomes the EMA initiative of clarifying the practical application of ethical standards in the context of EMA activities and supports European ethics and GCP principles to be implemented in all clinical studies submitted in the EEA.
- EGA supports the need for clinical data obtained through clinical trials approved by truly independent Ethics Committees and National Regulatory Authorities
- EGA welcomes the identified need for co-operation between international regulatory authorities in this sphere and measures to ensure robust framework for planning, oversight and conduct of clinical trials
- The title of the Reflection Paper only refers to the EMA, although it should read "to the EU regulatory authorities"

Clinical Trial Subjects

- **Attention should also be paid to clinical studies in healthy volunteers (non-therapeutic studies)**
  - specific subject characteristics related to recruitment and protection of vulnerable subjects
- **Confidentiality of trial subjects**
  - applicable laws and regulations differ among different regions, even within the ICH context – needs harmonization
- **Definition of the EEA population(s)**
- **Definition of vulnerable/dependent patients/populations**
  - definition of requirements and procedures acceptable for their enrolment
- **Specific requirements for a witness of the informed consent (?), as mentioned in section 5.2.**

Ethics Committees

- **Must have the right to monitor ongoing studies**
  - measures to implement this
- **Obligation to submit the study protocol for ethical and scientific review to an ethics committee that operates within an established regulatory network in addition to ethics committee in the third country**
  - definition of such countries is needed
- **If a sponsor does not foresee access of the product to the population in a country where it plans to conduct a study, should such a country be avoided?**
- **Specification of a "truly" independent ethics committee**

Scientific Advice from EU Regulatory Authorities

- A potent preventive power in terms of avoidance of ethics/GCP non-compliance
- To be used more often prior to conduct of clinical trials (define study design, endpoints, study population, use of placebo, active comparator, etc.)
- If mandatory, a definition of exceptions needed (e.g. conventional bioequivalence studies in healthy subjects with a straightforward design)
- Feasibility studies to be completed before submission of a request for a Scientific Advice?
- Regulatory requirement for the use of placebo (assay sensitivity) must not prevail over ethics in the common clinical practice within the EU.

GCP Inspections

- **The fact itself that the study is conducted solely outside the EU should not be a trigger for an inspection**
  - Numerous bioequivalence studies are conducted at well-established facilities outside the EU without any ethics/GCP concern
- **Definition of unexpectedly low levels of (S)AE reporting that will trigger the GCP inspection**
  - e.g. in case of a known/safe compound in a bioequivalence or therapeutic equivalence study
- **If remedies for general non-compliance issues due to misinterpretation of the guideline are drafted, they should be taken up in a Q&A open to public. It would provide further clarification for further sponsors.**

European Public Assessment Reports (EPARs)

- **EPAR should describe clinical trials included in the MA dossier, listing the trials and details concerning their conduct**
  - specification of “details”
- **Applicability of the trial to the EEA population should be demonstrated**
  - needs a definition of the EEA population
- **Assessment of the ethical issues and GCP compliance of the trials in the MAA**
  - applicable to and to be conducted separately for each clinical trial to support MAA (?)

Other issues

- Does the Reflection Paper cover both interventional and non-interventional trials?
- Every location of a clinical trial should be appropriately justified (Section 4)?
- Sponsors have QA systems in place to eliminate difference in quality standards, these are actually never expected due to various locations of clinical trials, as would imply from Section 4.
- “Validity” of selected comparators needs to be specified, since only studies with comparators procured on the EU market are acceptable for the EU application
- Is there a risk of an inaccurate statistical hypothesis (?) - Scientific Advice should eliminate the risk
- Concern about the stability of IMP (?) - mandatory temperature monitoring, CoA of IMP clear this
- Definition of measures for the consequences of non-compliance with GCP and ethical concerns included in the MAA to be made public

Conclusions

- Significant step forward in terms of supervision of clinical trials conducted in “third” countries, used for MAAs within EU
- Further clarification based on comments from involved parties needed
- Repetition of wording in certain parts to be minimized
- Definitions of certain terms required

The role and persepective of EDCTP on the regulation of clinical trials in third countries

European Medicines Agency (EMA)

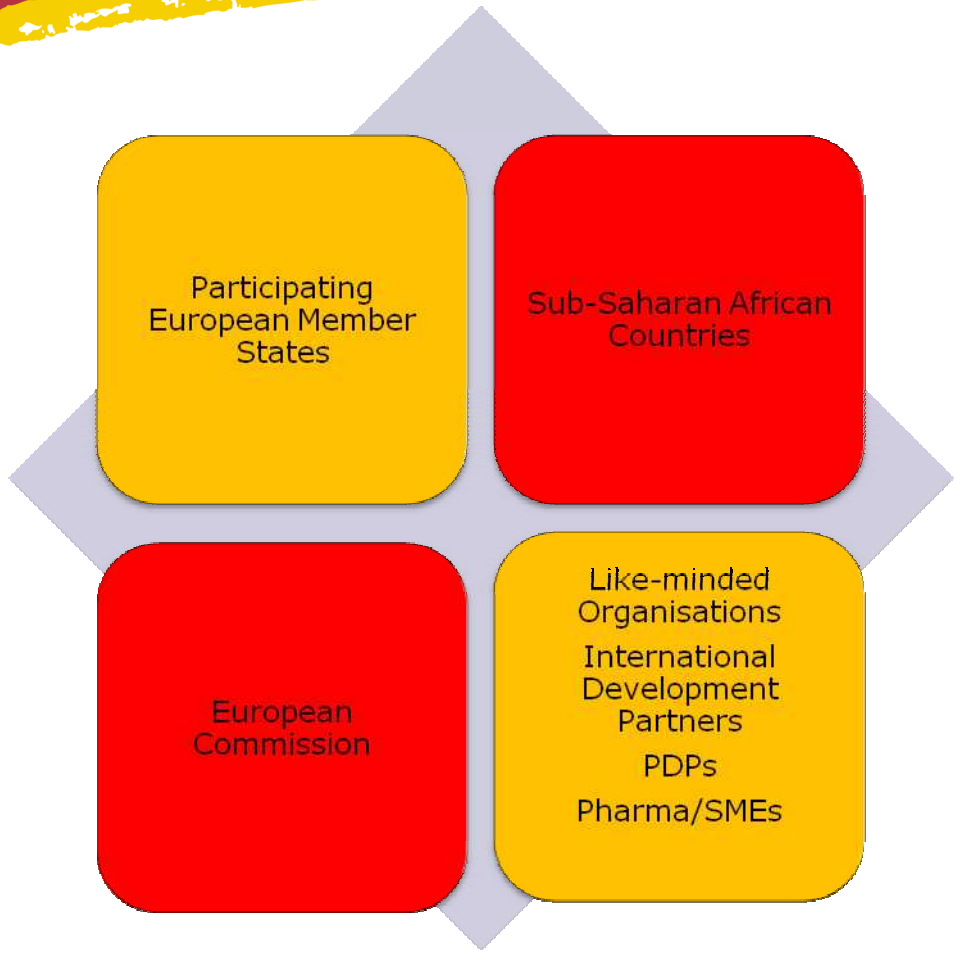
6-7 September 2010

International Workshop: Draft reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted for Marketing Authorisation Application to EMA

Charles S Mgone

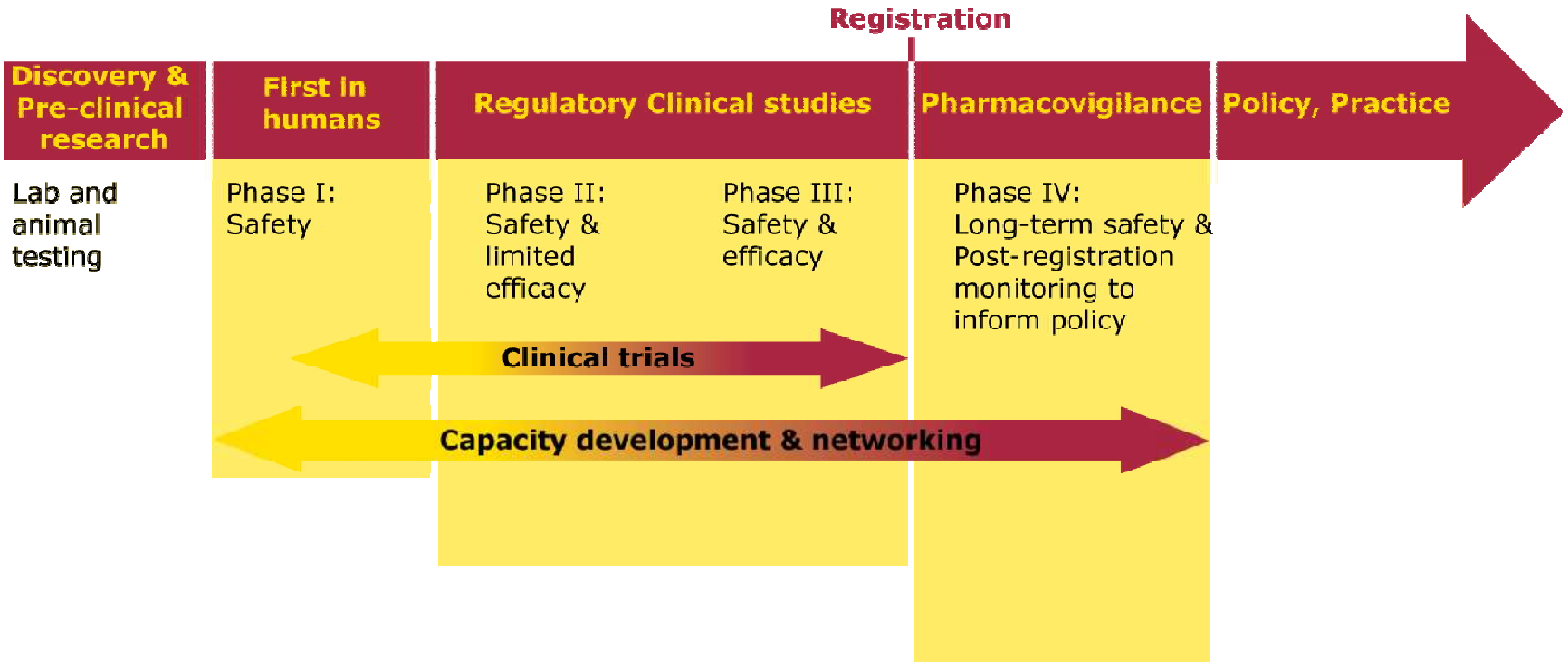
EDCTP Executive Director

Working in partnerships



- Coordination of national programmes
- Partnerships
- Clinical trials
- Capacity development
- Networking
- Fostering synergy

EDCTP Scope


Registration
Discovery & Pre-clinical research
First in humans
Regulatory Clinical studies
Pharmacovigilance
Policy, Practice
Lab and animal testing
Phase I: Safety
Phase II: Safety & limited efficacy
Phase III: Safety & efficacy
Phase IV: Long-term safety & Post-registration monitoring to inform policy
Clinical trials
Capacity development & networking

Limitations in the regulation of clinical trials in third countries

- Lack of capacity and competence in the ethics review mechanism and Regulatory framework
  - Lack of administrative capacity
  - Lack of essential structure (premises, equipment, funds, procedures, etc)
  - Confusions in the roles Ethics Review Committees and Regulators
- Inadequacy of insurance coverage and compensation
- Poor registration of clinical trials

Distribution of Ethics Review Committees (ERCs) in Africa

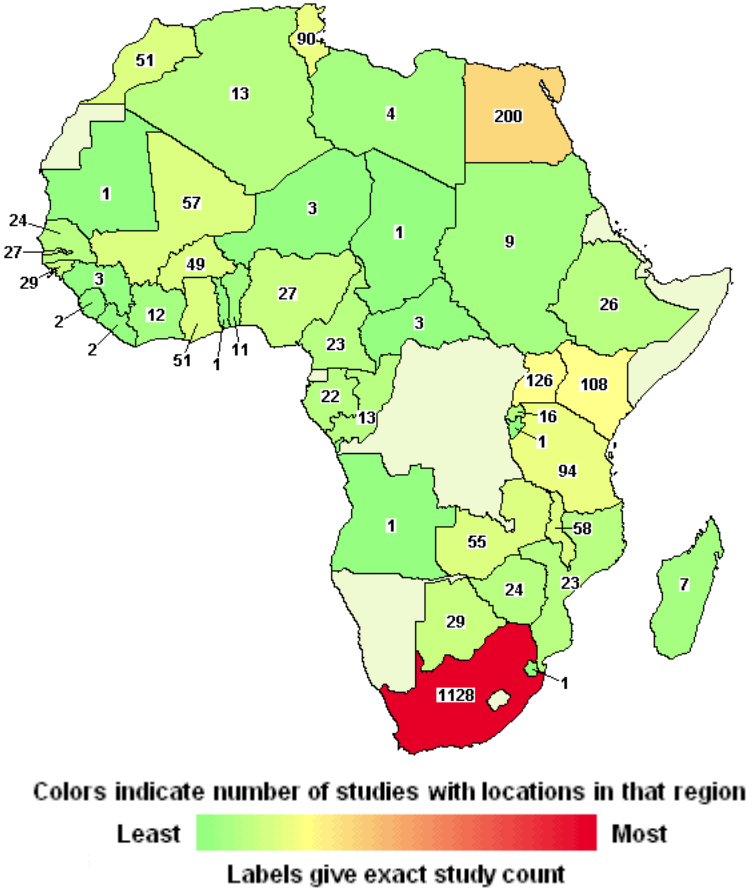
Number ERCs/Region	
Southern Africa	47
Eastern Africa	37
Western Africa	35
Northern Africa	16
Central Africa	10

Source: COHERED

Registered ongoing clinical trials

Worldwide	94,881
USA	49,294
Europe	23,398
Middle East	3,525
South America	2,919
Africa	2,052
South Asia	1,592
Central America	1,396

Source: *ClinicalTrials.gov*

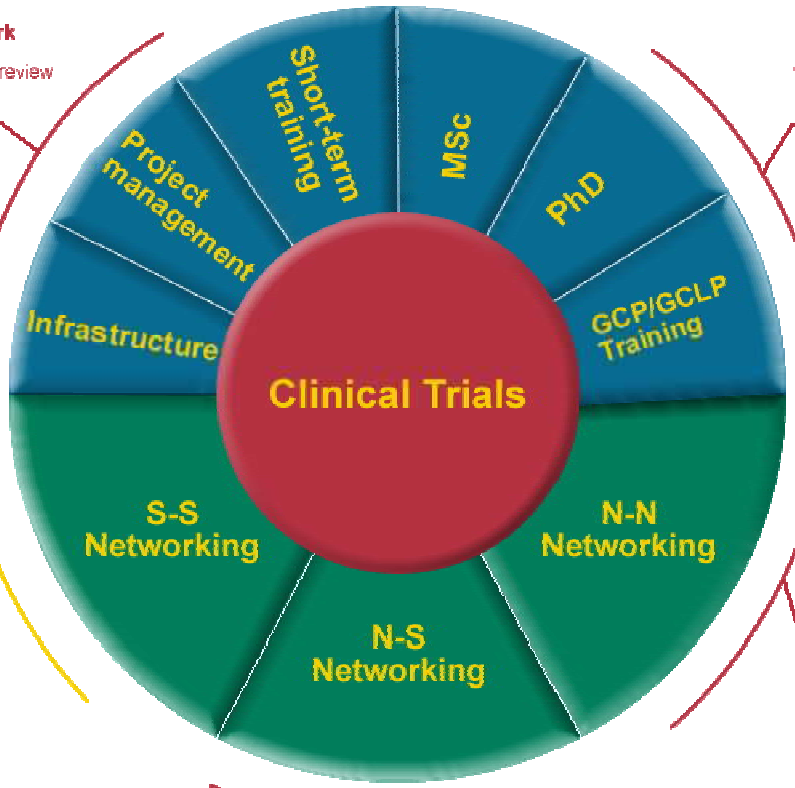


The EDCTP approach on capacity development

Ethics review
- Operational support
- Training (e-based/workshops)
- Mapping

Regulatory framework
- AVAREF
- Harmonisation and joint review
- Training

Clinical trials registry
- Collaboration with NRA and ERC



Site preparation & networking

Networks of Excellence
- Capacity Building
- S-S / N-N networking
- Synergy with other networks

Senior Fellowships

Current EDCTP support

- African Vaccines Regulators' Forum (AVAREF)
  - Joint review and inspection, training
  - Harmonisation of National Regulatory Authorities
- Ethics review
  - Operations
  - Training – workshops, e-based courses: www.elearningtrree.org and www.amanet-trust.org
  - Strengthening of National Ethics Committee
  - Mapping African Ethics Research Capacity (MARC) www.researcheticsweb.org
- GCP and GCLP training
- Clinical trials registration
  - Pan-African Clinical Trials Registry PACTR www.pactr.org

Key recommendations to EMA

- Take the leadership role in coordinating international cooperation and synergy
- Have active participation in training, technical support and assistance to NRA in developing countries
- Take proactive role in joint reviews and inspection with NRA from developing countries using these occasions as part of the capacity development

Thank you

http://www.edctp.org

Gunilla Sjölin-Forsberg
Secretary-General
Council for International Organizations of
Medical Sciences

CIOMS
(Council for International Organizations of Medical Sciences)

- An international, NGO, created in 1949 by WHO and UNESCO, headquartered in Geneva
- To facilitate **and** promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary
- Members are national and international medical and scientific associations
- In conducting its work, CIOMS frequently involves senior scientists from national and international governmental regulatory authorities, academia and pharmaceutical companies in working groups
- CIOMS has cooperated closely with WHO activities involving bioethics, health policy and drug development

Conflict of interest

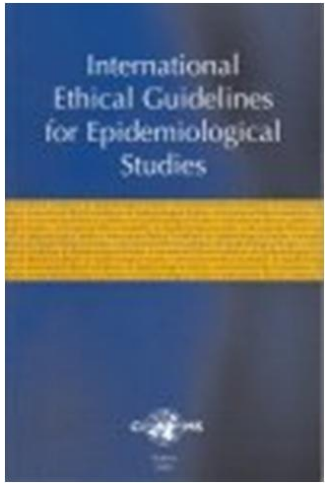
CIOMS

Funding Fees/Hospitality/ Contributions (Memberships Working Groups 2007-2010)

WHO

Asia Pacific Academy of Ophthalmology, EMA, **(EU), European** Heart Institute, I**nternational** College of Angiology, **International** Society of Audiology, **International** Association of Bioethics, **International** Society of Internal Medicine, **International** Federation of Clinical Neurophysiology, **International** Federation of Otorhinolaryngological Societies**, IFPMA**, **International** Society of Pharmacoepidemiology (ISPE), **International** Society of Pharmacovigilance (ISOP), **International**l Rhinologic Society, **International** College of Surgeons, **International** Federation of Clinical Chemistry and Laboratory Medicine, **International** Council on Alcohol and Addictions, **International** Council for Laboratory Animal Science (ICLAS), **International** Society of Hepatic Encephalopathies & Nitrogen Metabolism (ISHEN), **International** Union of Microbiological Societies, **International** Union of Nutritional Sciences (IUNS), **International** Association of Oral Pathologists, **International** Union of Physiological Sciences, **International** Medical Sciences Academy, **International** Federation of Medical Student Associations, Medical Women's **International** Association, The **World** Association for Medical Law, **World** Allergy Organization, **World** Association of Societies of Pathology and Laboratory Medicine (WASPaLM), **World** Federation of Chiropractic (WFC), **World** Federation for Ultrasound in Medicine and Biology, **World** Medical Association, **World** Organization of Family Doctors (WONCA), **World** Organization of Gastroenterology, **World** Psychiatric Association, **World** Veterinary Association, Abbott, Academy of Medical, Dental and Pharmaceutical Sciences of **Japan,** Afssaps (**France),** American Society for Bioethics and Humanities, **American** College of Chest Physicians, Amgen, Artage (**Japan**), Association of the Scientific Medical Societies in **Germany,** AstraZeneca, Bayer-Schering, Berna Biotech/Crucell, BfArM (**Germany),** Bio-Manguinhos (**Brazil**), Boehringer-Ingelheim, CDC Atlanta (**USA)**, Centre Scientifique de **Monaco,** Comité des Académies Royales de Médecine, **Belgium,** Consulta di Bioetica, **Czech** Medical Association, Eisai **(Japan**), FDA (**USA)**, Federation of **Polish** Medical Organizations Abroad, Federation of **Polish** Medical Societies, GlaxoSmithKline, Good Clinical Practice - Alliance, Group for the Respect of Ethics & Excellence in Science (GREES), GSKBio, Health **Canada**, , Islamic Organization for Medical Sciences (IOMS), **Kuwait,** Ingenix**,** J&J, Jannsen Cilag, **Korean** Academy of Medical Sciences, Lilly, Merck, MHRA (**UK)**, MSSO, National Fund for Scientific Research (NSFR, **Belgium**), Novartis, Pfizer, PMDA (**Japan**), **Polish** Academy of Sciences, PT Bio Farma (**Indonesia**), Purdue Pharma L.P., Roche, Royal **Netherlands** Academy of Arts and Sciences, Sanofi-Aventis, Sanofi-Pasteur, Schering-Plough, Science Council of **Japan,** Serum Institute of **India**, SJM/JOM **(Japan**), **Slovak** Medical Association, **South African** Medical Research Council, **Swiss** Academy of Medical Sciences, The **Israel** Academy of Sciences and Humanities, The Research Council for **Norway**/The National Committee for Medical Research Ethics, The Royal **Danish** Academy of Sciences and Letters, The **Swedish** Medical Research Council, Union of the Scientific Medical Societies of **Bulgaria,** Wyeth.

Examples of some major CIOMS activities relevant to this Workshop:



In 2009, published updated version of "The International Ethical Guidelines for Epidemiological Studies" Follows the format of the guidelines for Biomedical Research, which are familiar to research ethics committees. Addresses the special problems that arise in public health research, epidemiology including pharmacoepidemiology. Adds coverage of research on stored human biological samples, among other topics

In 2002, published the 2nd edition of "The International Ethical Guidelines for Biomedical Research Involving Human Subjects . Elaborates the Declaration of Helsinki and provides commentary on the principles and greater detail on procedures. Is widely used by investigators & research ethics committees around the world, especially in developing countries (see: www.cioms.ch)

Comments on the EMA Reflection Paper
Ethics committees

Ethics committees in sponsoring and hosting countries

EMA draft 3.2…"When the sponsor is an international organisation, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards and the research protocol should be submitted for ethical and scientific review in the country of the sponsoring organisation and the ethical standards applied should be no less stringent than they would be for research carried out in that country.

This statement is according to *Guideline 3 of the 2002 CIOMS Guidelines and 2009 CIOMS Guidelines for Epidemiological Studies that also includes:* "The health authorities of the host country as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards"

CIOMS: Try to more clearly describe roles and duties of the two different committees with regards to special responsibilites ie:

- scientific methods
- adequate standards of safety
- justification for choice of host, method used for informed consent
- health needs/priorities in host countries
- potential compliance
- etc

Comments on the EMA Reflection Paper
Informed Consent Procedure

EMA draft 3.2 Information/Consent procedure

Guideline 5 of the CIOMS 2002 Guidelines (pages 37-39).Guideline 5 of the 2009 CIOMS Guidelines for Epidemiological Studies:

Obtaining informed consent: Essential information for prospective research subjects

- CIOMS: It would be valuable if the EMA paper could list "key elements of information" provided to potential subjects prior to informed consent ie:
  - participation voluntary
  - purpose of research, procedures and how it differs from routine
  - expected duration,
  - direct benefits, if any, expected to result to subjects participating
  - any foreseeble risk, pain or discomfort
  - expected benefits contribution to community, society or science
  - whether, when and how products/interventions studied will be made available post-trial to subjects and if required to pay for them
  - etc

Comments on the EMA reflection paper
Informed consent procedure

EMA draft 3.2 Information/Consent procedure

Guideline 4,16 of the 2002 CIOMS Guidelines and 2009 CIOMS Guidelines for Epidemiological Studies

- CIOMS: Describe variation in traditions and attitudes in third countries related to individual informed consent:

  - Prior consultation of family (Japan, China)
  - Group/Community consent or consent by a village leader (some African countries)
  - Womens right to consent questioned

    A spouse or partner may replace?

    Acceptance?/Recommended solution?

Comments on the EMA reflection paper

Choice of control in Clinical Trials (use of placebo)

EMA draft 3.6 Placebo and active comparator

Guideline 8, 11 of the 2002 CIOMS Guidelines and 2009 CIOMS Guidelines for Epidemiological Studies

- It is emphasized in the reflection paper that studies carried out in third countries should follow the same principles in terms of placebo use as studies carried out within EU

- CIOMS: In addition, suggest to further specify in the draft:
  - Give examples of studies where placebo use is not accepted and when it is accepted (no proven intervention exists, scientifically needed, mild conditions/minor risks, reserve/"escape treatment" provided, placebo duration minimized.
  - Discuss the justification in relation to the need of performing the study in third countries

Comments on the EMA reflection paper

Address access to study drug after the trial

EMA draft 3.7 Access to treatment post trial

Guideline 5 of the 2002 CIOMS Guidelines and Guideline 10 of the 2009 CIOMS Guidelines for Epidemiological Studies

One important point related to clinical trials in third countries is: -whether, when, how and how long any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them

- Address if the view on this of the ethics committe in the host country is requested to be part of the protocol and (in line with § 14 of the Declaration of Helsinki)
- Include in information to patient prior to consent

Additional comments from CIOMS on the EMA reflection paper

- **Please correct references to CIOMS documents:** These should be referred to as "*Guideline (Number) of the 2002 (or 2009) CIOMS Guidelines*
- Is the **ambition to cover also epidemiological** (interventional /noninterventional) **research?** Epidemiological studies are key instruments to study vaccine efficacy and safety (Guidance in CIOMS International Ethical Guidelines for Epidemiological Studies published in 2009) and in pharmaco-epidemiological drug safety studies.
- 3.1 (lines 268-272): "Where a clinical trial is to be conducted…. the sponsor should consider submitting the study protocol … to an ethics committee(s) that operates within an established regulatory framework with ethical standards equivalent to those applying in the EU, in addition to doing to in the country concerned by the trial." CIOMS proposes this as a routine practice, **replace "sponsor should consider submitting"** with "**sponsor should submit**". CIOMS proposes that in this situation the protocol should be submitted to an **ethics committee of the sponsor´s country** as well as to an ethics committee of the host country for ethical and scientific review.

Additional comments from CIOMS on the EMA reflection paper

- The ethics committee in the country where the trial is to be conducted should have, as either members or consultants, persons with understanding of the community's customs and traditions. EMA 3.1: *" Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects and to advise on whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange and other customs and traditions". (lines 296-299)*.

- CIOMS: The person should also be able to determine the acceptability of the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as of the means proposed to protect the welfare of the research subjects (*Guideline 3 of the 2002 Guidelines and 2009 CIOMS Guidelines for Epidemiological Studies)*

Additional comments from CIOMS on the EMA reflection paper

- *EMA 3.5 Vulnerable populations*

  Clinical research on children (lines 544-614)
- *Guideline 14 of the 2002 and 2009 CIOMS Guidelines*
- CIOMS comment: The document should address informed consent/ethics in/of pure pharmacokinetic studies (comparative studies on bioavailability of an original and a generic product) in healthy children *(the research might not equally well be carried out with adults; the purpose of the research is to obtain knowledge relevant to the health needs of children).* In connection with treatment of a disease concerned parents may consent on behalf of a sick child but using healthy children for these studies -not benefiting the child but causing a potential risk - needs clarification/statement in the document. Money (inducement) in poor countries may adversely influence on parents and allow their children to participate!

Final comments from CIOMS on the EMA reflection paper

- ***5.1 Review procedure (979-984)***

  The CHMP proposal for the establishment of a pool of experts supporting the CHMP in its assessment of the ethical aspects of CTs submitted with the MAA could be set up

- ***Resources EMA 6.3.3 (1409-1433)***

  The establishment of a "Service" or "Centre" that could enable sharing – (page 39)

- **CIOMS would be willing to volunteer**
- **If appropriate CIOMS may establish a group of experts in research ethics if EMA wants help in interpretation of CIOMS Guidelines in specific cases/situations.**
- **If appropriate CIOMS could organize (but not fund) a workshop**

F.I *Joint CIOMS/WHO Drug Development Research in Resource-limited countries:* How to succeed in implementation of Good Clinical Practice Guidelines *Draft report* from 2005 available at the website of CIOMS **(www.cioms.ch).** An updated core group is under development and an initial meeting was held 4 June 2010 with the purpose to update and finalize the *Draft report.*

Session 5: International organisations perspective on the Draft Reflection Paper and their plans for the future

Council of Europe perspective

Dr Laurence Lwoff
Head of Bioethics Division
Council of Europe

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Council of Europe

- Objective of CoE activities:
  - Protection of individual rights and freedoms in the field of biomedical research
  - Legally binding international instruments elaborated by 47 members states:
    - Convention on Human Rights and Biomedicine
    - Additional Protocol concerning Biomedical Research
- Research should be carried out freely subject to provisions for the protection of human beings
  - Close relationship between scientific quality and ethical acceptability
- Particular concerns in relation to research in « third countries »:
  - Same standards of protection of all participants
  - Avoiding double standards (Article 29 of the Additional Protocol)

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Key points

- Measures to be taken before trial starts
  - Key importance:
    - **Ethical evaluation of research project**
    - Research ethics committees
    - Double review?
  - Legal security (including possible measures following serious breach of fundamental principles)
- International cooperation/coordination

Ethical evaluation of research project
Research ethics committees

- Research ethics committee in countries where research takes place
  - **Independence**
  - Multidisciplinarity (?)
  - Competence (?)

- Information to be provided
  - Consent process
  - Placebo (justification)
  - Access to treatment post-trial
  - Reasons for location of the clinical trial and for potential participants considered

Key recommendations (Chapter 6)

- Submission of research project to an independent ethics committee
  - Support for capacity building in host countries – targeted interventions to real needs (independence)
  - Support for establishment and strengthening ethics committees (independence)
  - Synergies/Cooperation

Council of Europe activities – Possible cooperation (Ethical review - Capacity building)

- **Targeted action** in countries
  - DEBRA programme
    - Bilateral/regional seminars/training
    - Legal expertise (e.g. Georgian Law on biomedical research)
    - Targeted programme
      - Currently considered: Croatia, Ukraine, Russia

- **Development of tools** to facilitate implementation of ethical principles in biomedical research (laid down in European legal instruments)
  - Guide for research ethics committee members
  - Project: guide focusing on specific research field e.g. research on biological materials

- *Elaboration of a* ***Declaration on ethics of biomedical research in countries with developing and emerging economies***
  - Basis: Article 29 of the Additional Protocol
  - 47 CoE member states
  - Australia, Canada, Israël, Japan, USA, Mexico
  - European Commission, UNESCO, WHO

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

International Workshop on Draft Reflection Paper On Ethical And GCP Aspects Of Clinical Trials Of Medicinal Products For Human Use Conducted In Third Countries And Submitted In Marketing Authorisation Applications To The EMA

EMA, London, 6 and 7 September 2010

Perspective of the World Medical Association (preliminary)

Otmar Kloiber
Secretary General
World Medical Association

World Medical Association

Roof organization of the
national medical associations

Setting the global ethical standards for medicine

Key policy in this area is the
Declaration of Helsinki –
Ethical Principles for Medical Research
Involving Human Subjects

Requested Viewpoints

International cooperation including in particular capacity buildings and the future plans for their organizations
Guidelines in the area covered by the Draft Reflection Paper

(Chapter 6).


Global Migration of Physicians

Perspectives

We welcome the approach by EMA

Participation in clinical research is crucial for the development of health care systems

Suppressing/withholding research in/from poorer countries is no answer

Recognition by leading agencies provides stimulus and support for national development

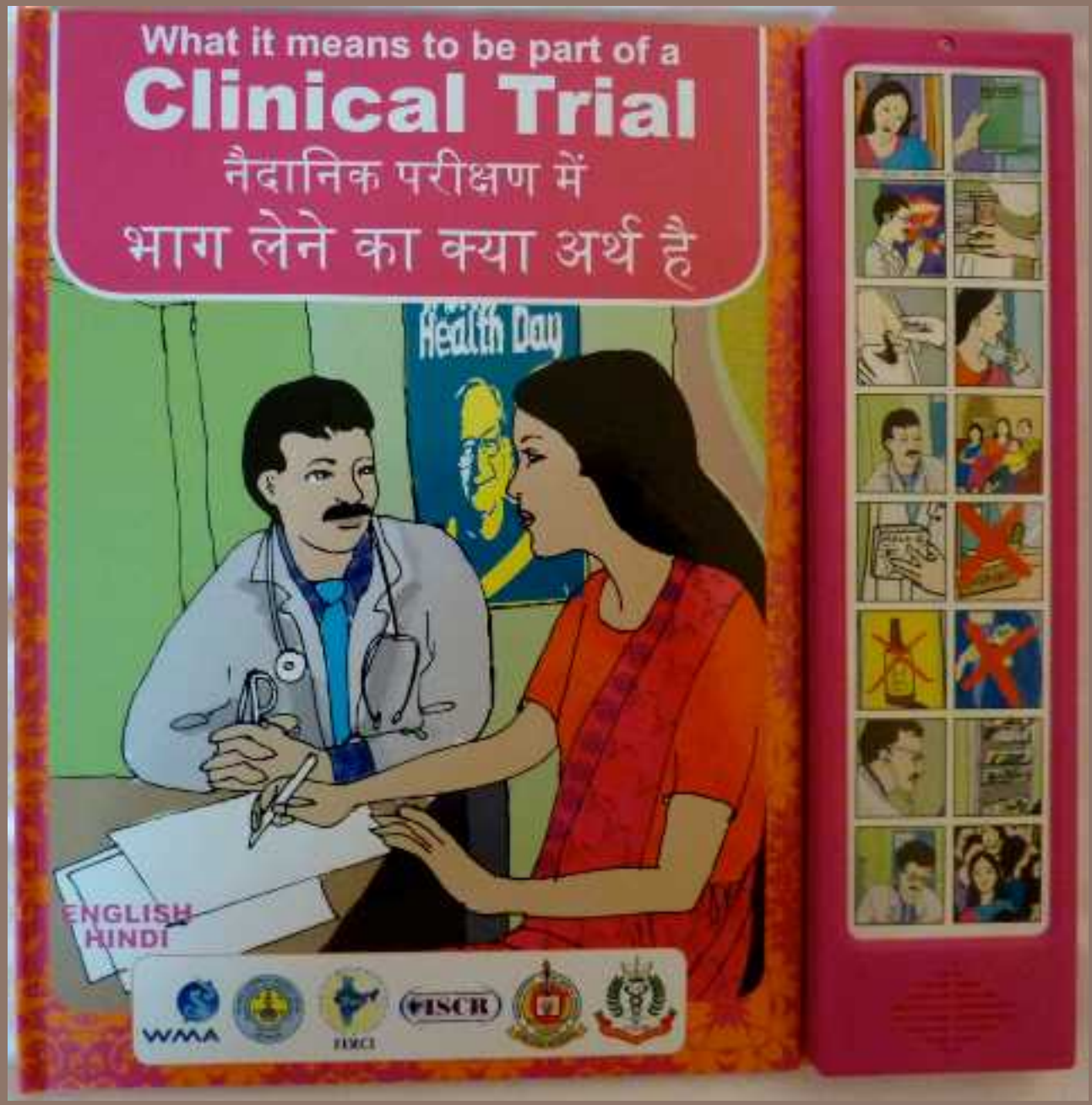
Patients and professionals will benefit from the "side-effects" of properly conducted research

Caveats

The draft mentions only a few ethical principles and requirements that are important (others are implicit?)

The European Union has no right to dictate others their ideas about ethics - but the approach to apply same globally consented standards is correct

The applied principles should be agreed internationally by institutions duly mandated


What it means to be part of a
Clinical Trial
नैदानिक परीक्षण में
भाग लेने का क्या अर्थ है
Health Day
ENGLISH
HINDI
WMA
FISCR

Recommendations

The anticipated support = well invested money

Building sustainable change - fostering the application of ethical principles and standards

Not to be restricted to the ethical principles and standards mentioned

Support should be target physicians other health professionals, researchers, agencies and RECs

1:500

1:50.000

WMA

www.wma.net

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in MAA to the EMA

International cooperation in the regulation of clinical trials, their review and inspection, and capacity building in this area

EMA, London, 6-7 September 2010

Dr. Liliana Chocarro, WHO, IVB/QSS/Regulatory Pathways

Dr. Lembit Rago, WHO, QSM

Points of agreement

Emphasis on:

- International cooperation (information exchange, capacity building, interaction with trial target country regulators)
- Common international approach
- International network of clinical trial regulators
- Recognition of importance of requirement of national ethical and regulatory approval of trials outside EU/EAA
- Short and long term activities to ensure ongoing communications and cooperation with trial host countries

Highlights on proposed activities

- Chapter 6:International organization perspective
  - Short term activities
    - Establishment of a system for updated information on NRAs, ECs, GCP inspections, investigator support and training in priority countries, through a network of key contacts
    - Establishment of links with other organizations and initiatives
  - Long term activities
    - Establishment of a "center" for continued links with organizations related to clinical research and regulatory oversight of clinical trials

Suggestions for modifications and additions

- Why not evaluation under Article 58?
  - For vaccines, it is foreseen that most new vaccines will be developed for diseases endemic in developing countries
  - There would be great value in involving the regulators from trial host countries during the clinical development and then during the evaluation for Scientific Opinion
- GCP compliance is checked "after the fact", if the assessor of the MAA finds a trigger for GCP inspection.
  - Can EU create a requirement (recommendation) to notify of all trials to be conducted outside EU linked to MAs and Art 58 in advance?
  - Role of clinical trial registries and cooperation with them?
  - Consider co-inspections with host country Inspectorate during the trial

Key recommendations

- Establish a focal person at EMA to follow up on clinical trials in developing countries and discuss possible interactions/cooperation
- Establish a inter-institutional committee to link EMA and regulatory networks, i.e. DCVRN, AVAREF/PACTA through Secretariat.

WHO will support this and is ready to-discuss further the establishment of the proposed "center"

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

International cooperation in the regulation of clinical trials, their review and inspection and capacity buildings in this area- EMA Perspective

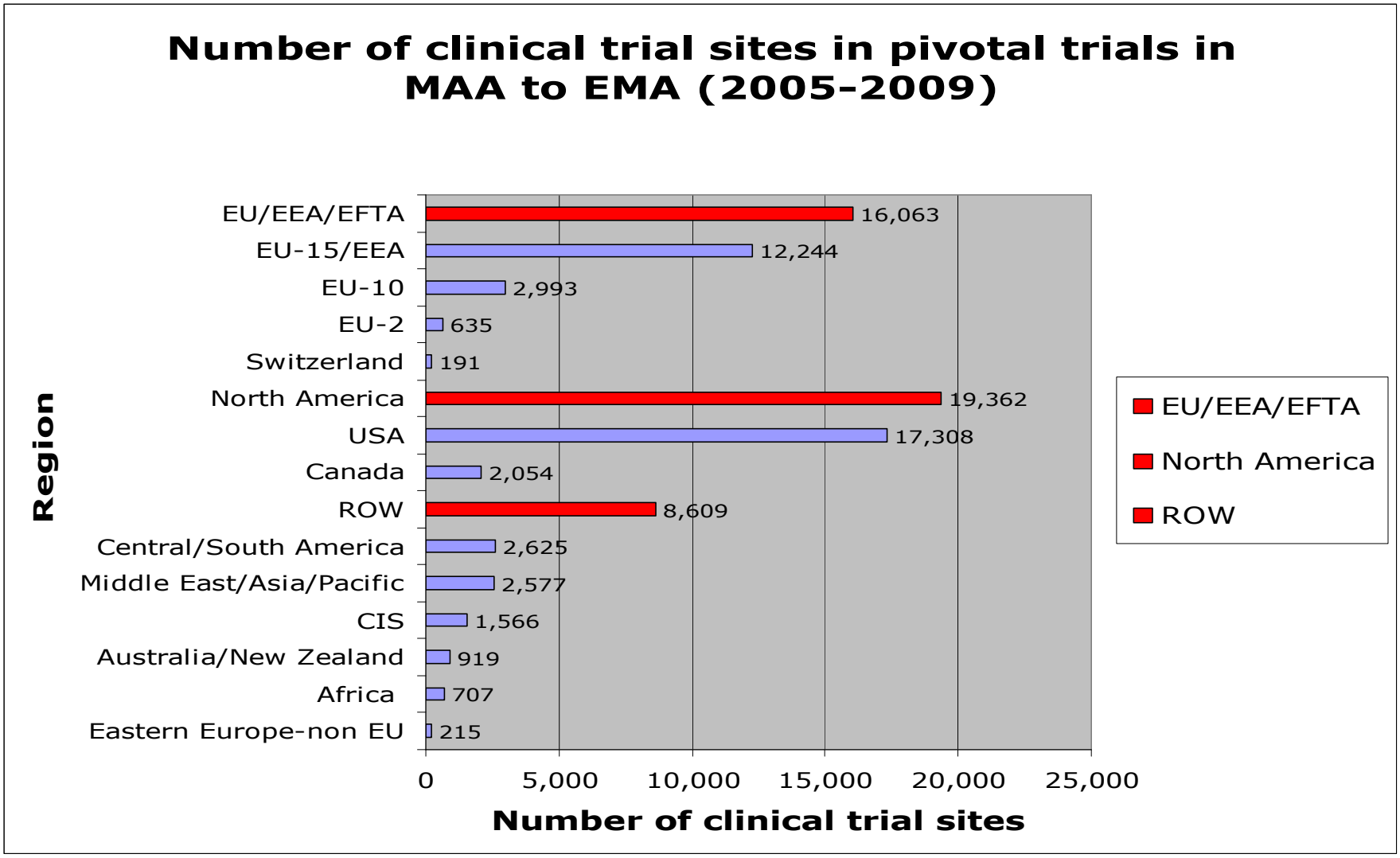
EMA International Workshop on the Reflection Paper "on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA 6-7 September 2010

Presented by: Ana Rodriguez
Head Clinical and Non-Clinical Compliance

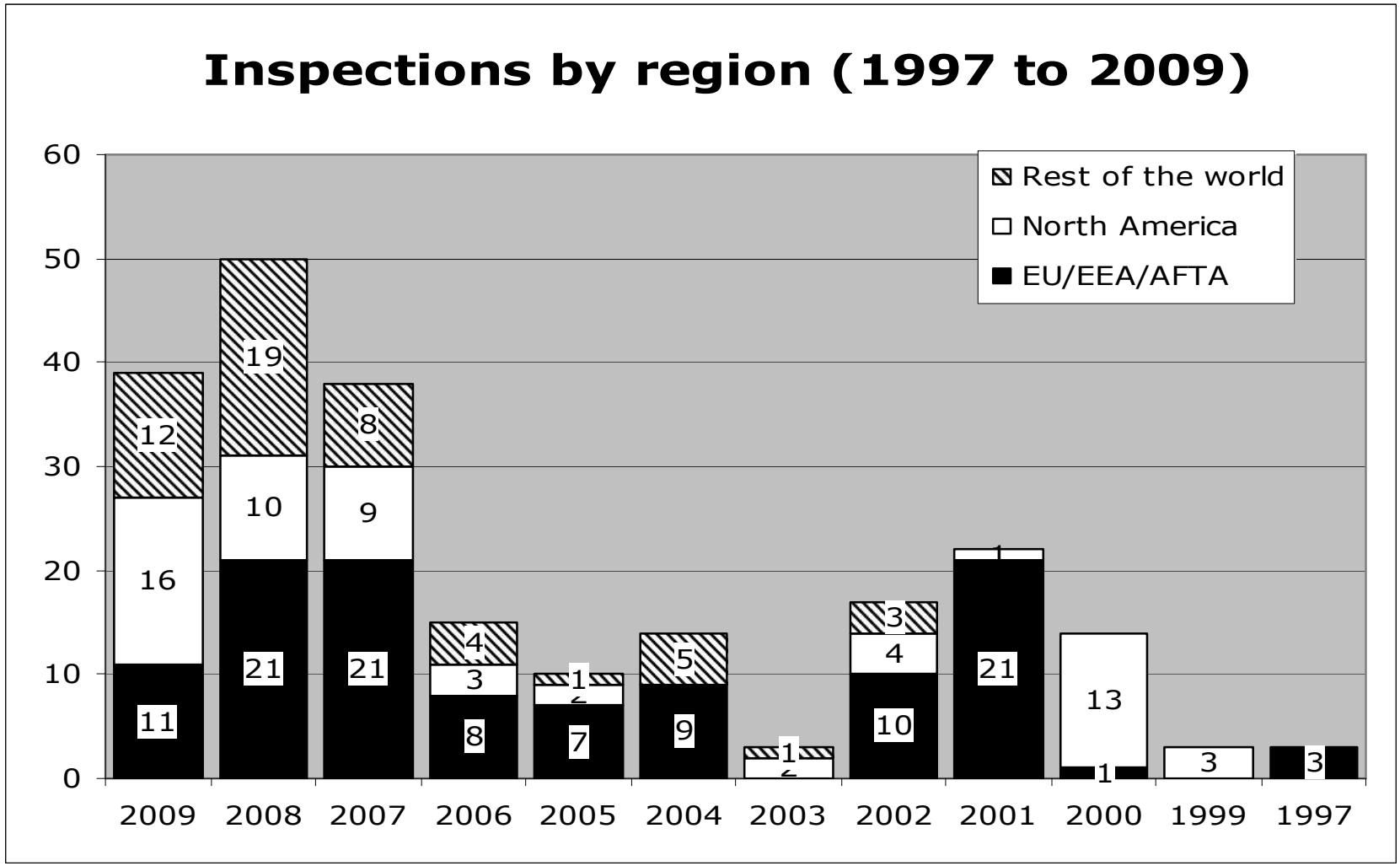
Current Context

- Globalization of clinical trials research
  - 61% of the patients in pivotal trials submitted in MAA to the EMA during the observation period from January 2005 to December 2009 were from non EU countries.
    - 35.2% from North America
    - 25.9% from the ROW region (Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe-non EU)
- Clinical trials are increasingly conducted in emerging growth regions
  - Central/South America (9.2%)
  - Middle East/Asia/Pacific (7.8%)
  - CIS (3.8%)
  - Africa (3.0%)
  - Australia/New Zealand (1.5%)
  - Eastern Europe-non EU (0.7%)

Current Context



Current context-CAP GCP Inspections

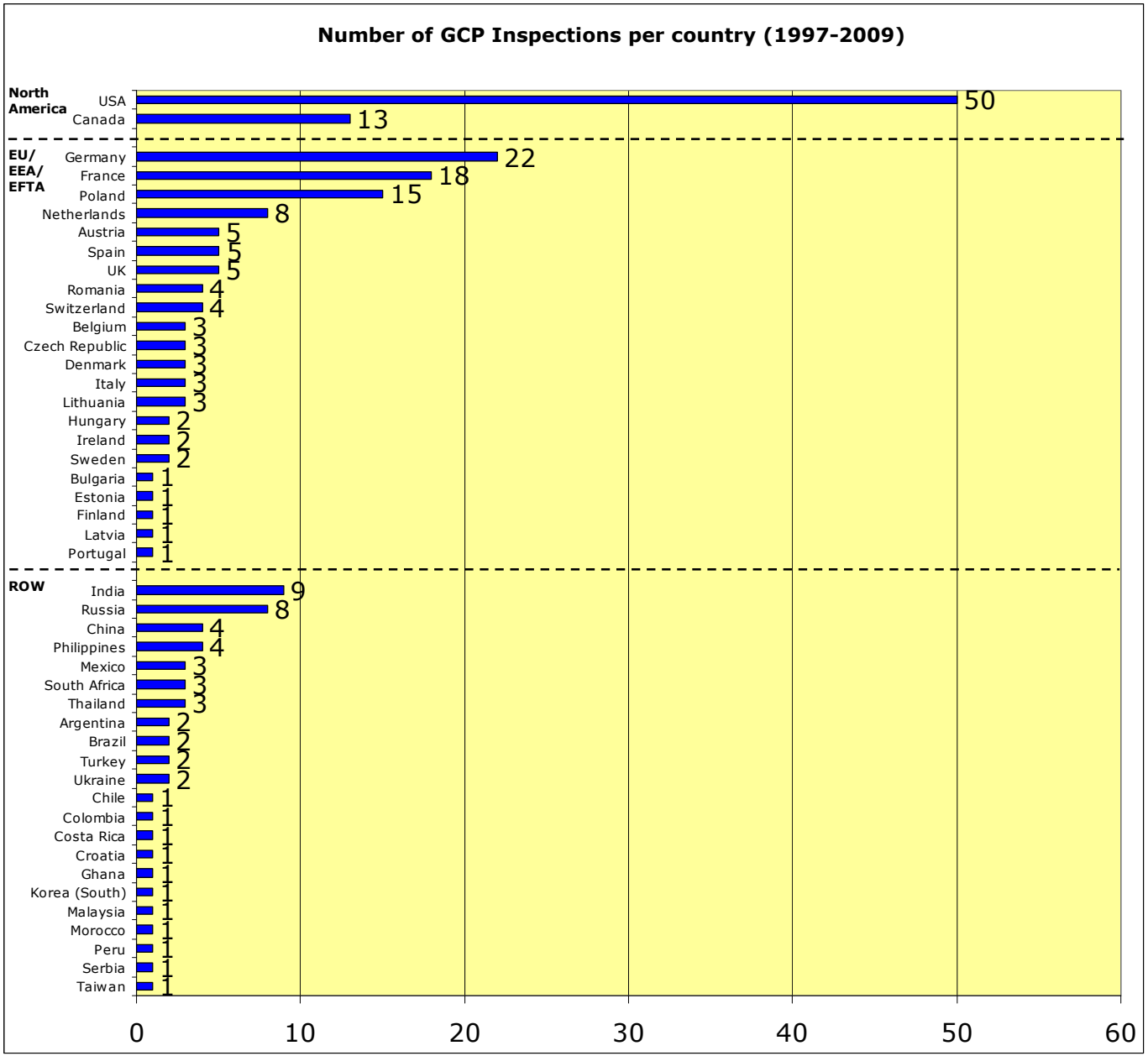


Current Context

- Limitation of available inspection resources
  - e.g. only a sample of sites and studies can ever be inspected
- Resources can be used more efficiently
  - Working in collaborative and synergistic manner
  - Facilitating information exchanges

Activities of the EMA Clinical and Non clinical compliance section

- Tracking the distribution of patients participating in pivotal trials included in Marketing Authorisation Applications (MAA) submitted to the Agency from 2005:
  - Identify those countries of interest for cooperation
  - To ensure greater supervision of the conduct and ethical standards of clinical trials performed outside the EU.
  - Report on Clinical trials submitted in marketing authorisation applications to the EMA: Overview of patient recruitment and the geographical location of investigator sites http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf


Number of GCP Inspections per country (1997-2009)
North America
USA 50
Canada 13
EU/ EEA/ EFTA
Germany 22
France 18
Poland 15
Netherlands 8
Austria 5
Spain 5
UK 5
Romania 4
Switzerland 4
Belgium 3
Czech Republic 3
Denmark 3
Italy 3
Lithuania 3
Hungary 2
Ireland 2
Sweden 2
Bulgaria 1
Estonia 1
Finland 1
Latvia 1
Portugal 1
ROW
India 9
Russia 8
China 4
Philippines 4
Mexico 3
South Africa 3
Thailand 3
Argentina 2
Brazil 2
Turkey 2
Ukraine 2
Chile 1
Colombia 1
Costa Rica 1
Croatia 1
Ghana 1
Korea (South) 1
Malaysia 1
Morocco 1
Peru 1
Serbia 1
Taiwan 1
0 10 20 30 40 50 60

Activities in relation to international cooperation on GCP inspections

- Participation of third country inspectors as observers in EU inspections performed in their territory
- Training activities: EU GCP IWG training courses (yearly basis)
  - 2007, 2008 and 2009: WHO
  - 2008: Argentina, Brazil, Ghana, South Africa and USA
  - 2009: Argentina, Australia, Canada, Ghana, India, Japan, Mexico, South Africa, Chinese Taipei and USA
  - 3-5 November 2010- London

Activities in relation to international cooperation on GCP inspections

- EMA FDA GCP Initiative- 18 Pilot phase
  - Periodic information exchange
  - Conduct Collaborative inspections
  - GCP related regulation, draft guidance and policy documents

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016818.pdf

- Leading the preparation of the reflection paper under discussion and organization of this international workshop
- Organization of the GCP Workshop on 8th September 2010

Future cooperation in the field of GCP inspections

- Proposal of an international network of regulators in conjunction with the WHO and ICH regulatory forum:
  - Agree, share and maintain a list of relevant contact points of interested regulatory authorities (participating countries or national, regional or international regulators)
  - Agree a system to exchange information:
    - Regulatory framework and system implemented for clinical trials oversight (laws, guidelines, policies etc.)
    - Links with other projects and initiatives to identify training/capacity building needs and avoid overlaps
    - Request on different issues: information, assistance/expertise, trainers, speakers etc.
  - Develop more comprehensive confidentiality frameworks for exchange of information between regulators

Other related EMA activities

- Appointment of International Liaison Officer – Emer Cooke – developing agency strategy
- Roadmap – 2010-2015 – Globalisation of clinical trials and of manufacturing
- Article 58 opinions – development with WHO
- Certificates of Medicinal Products
- GMP inspections in third countries – API initiative
- EudraCT public information – 4th quarter 2010
- Confidentiality arrangements
  - EU/USA, EU/Canada, EU/Japan, EU/Australia
  - Bilateral discussions between European Commission and China, India, Russia and WHO

The goal

- Helping each other, building expertise and systems
- Reducing duplication of effort
- Filling the gaps in the global network
- protect the rights, integrity and welfare of trial subjects

Thank you!

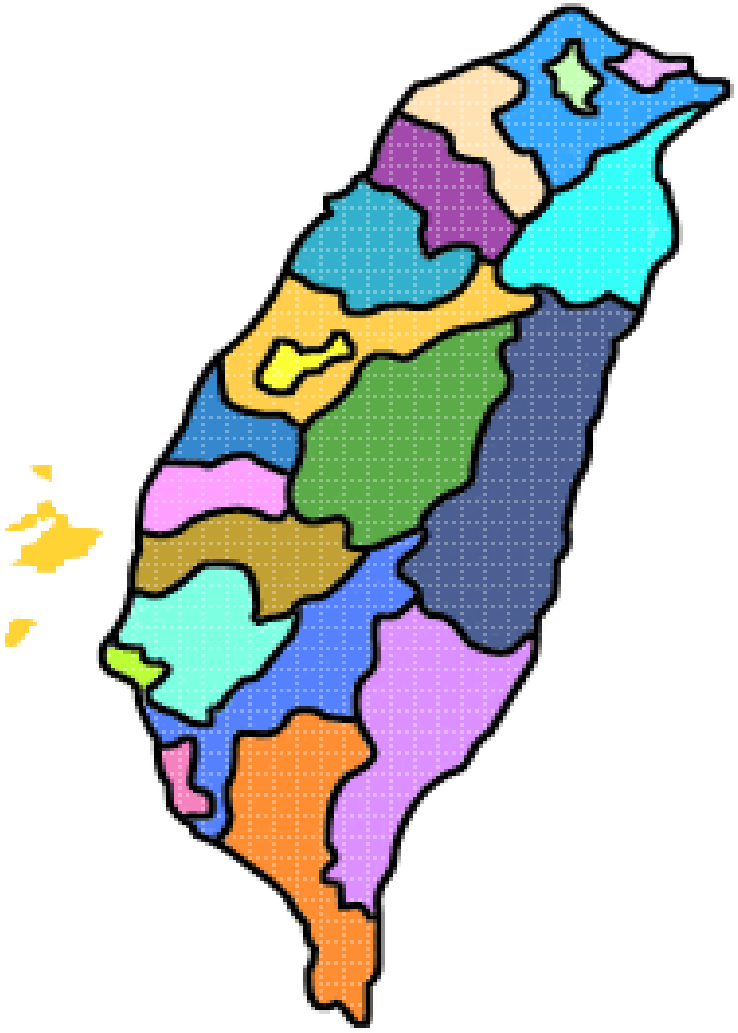
Status of GCP Laws/Regulations and Inspections in Taiwan

Chao-Yi Wang
Taiwan Food and Drug Administration
Department of Health, Taiwan

September 6 ~ 7, 2010

Taiwan - Geographic features

- Geographic features
  - South-eastern coast of Asia
  - Total area : 36,179 sq. km
  - Population : 23 millions
  - Population Aged over 65 :10.4%

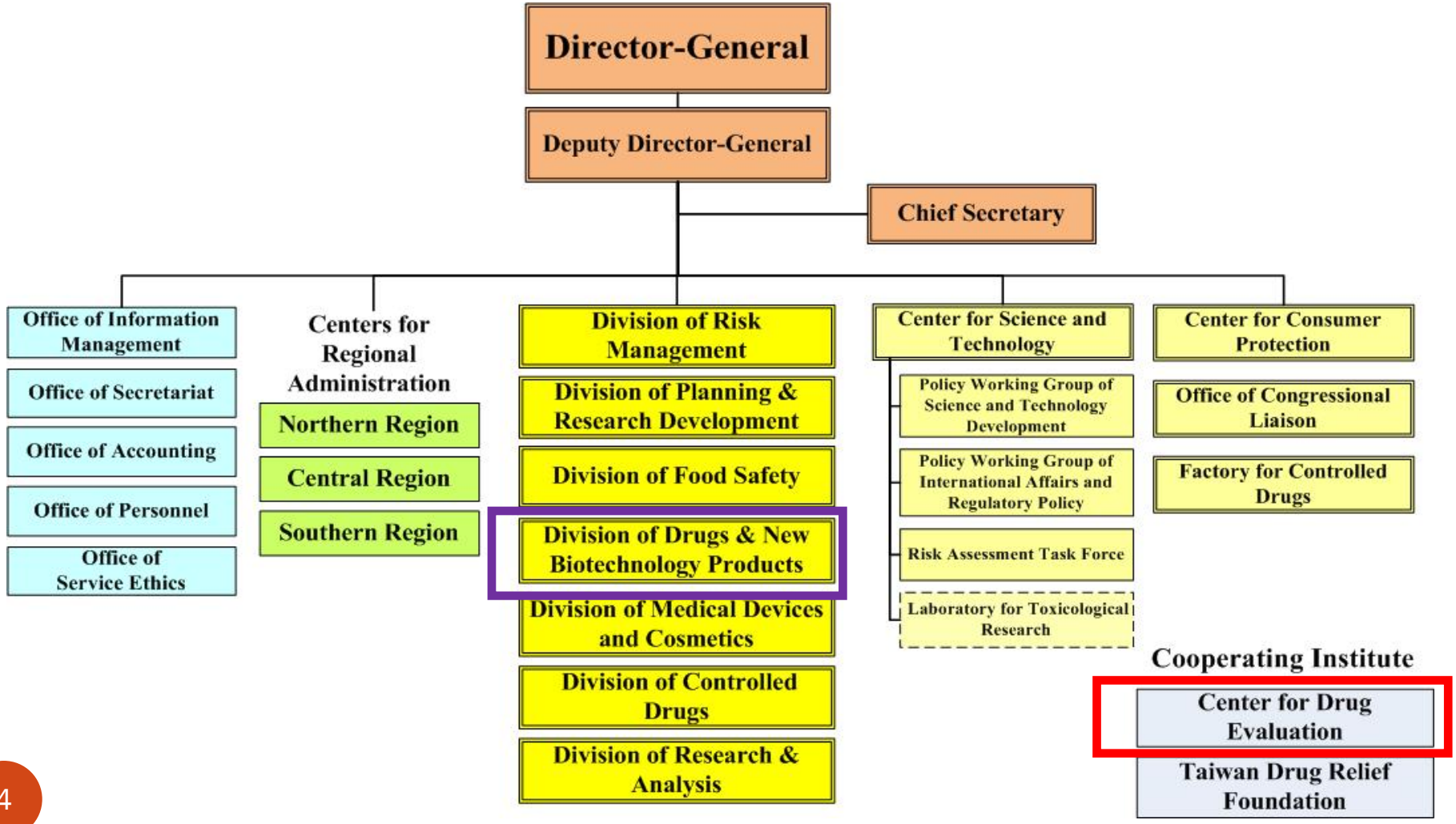


Establishment of Taiwan FDA

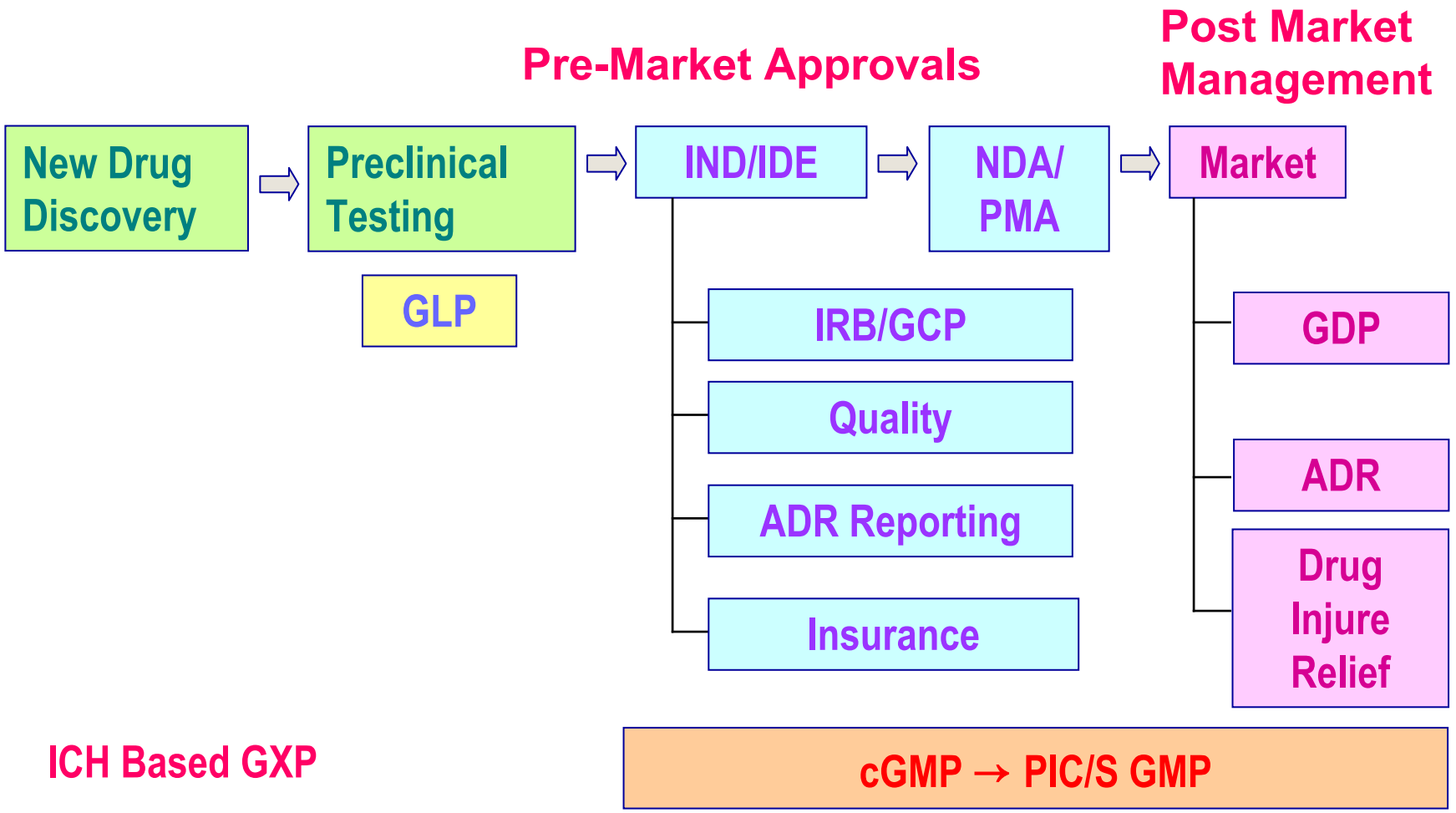
- Taiwan FDA (TFDA) was inaugurated on Jan. 1, 2010
- TFDA supersedes the following 4 bureaus of Department of Health
  - Bureau of Food Safety
  - Bureau of Pharmaceutical Affairs
  - Bureau of Food and Drug Analysis
  - Bureau of Controlled Drugs

TFDA Organization Chart

- Taiwan FDA (TFDA) was inaugurated on Jan. 1, 2010



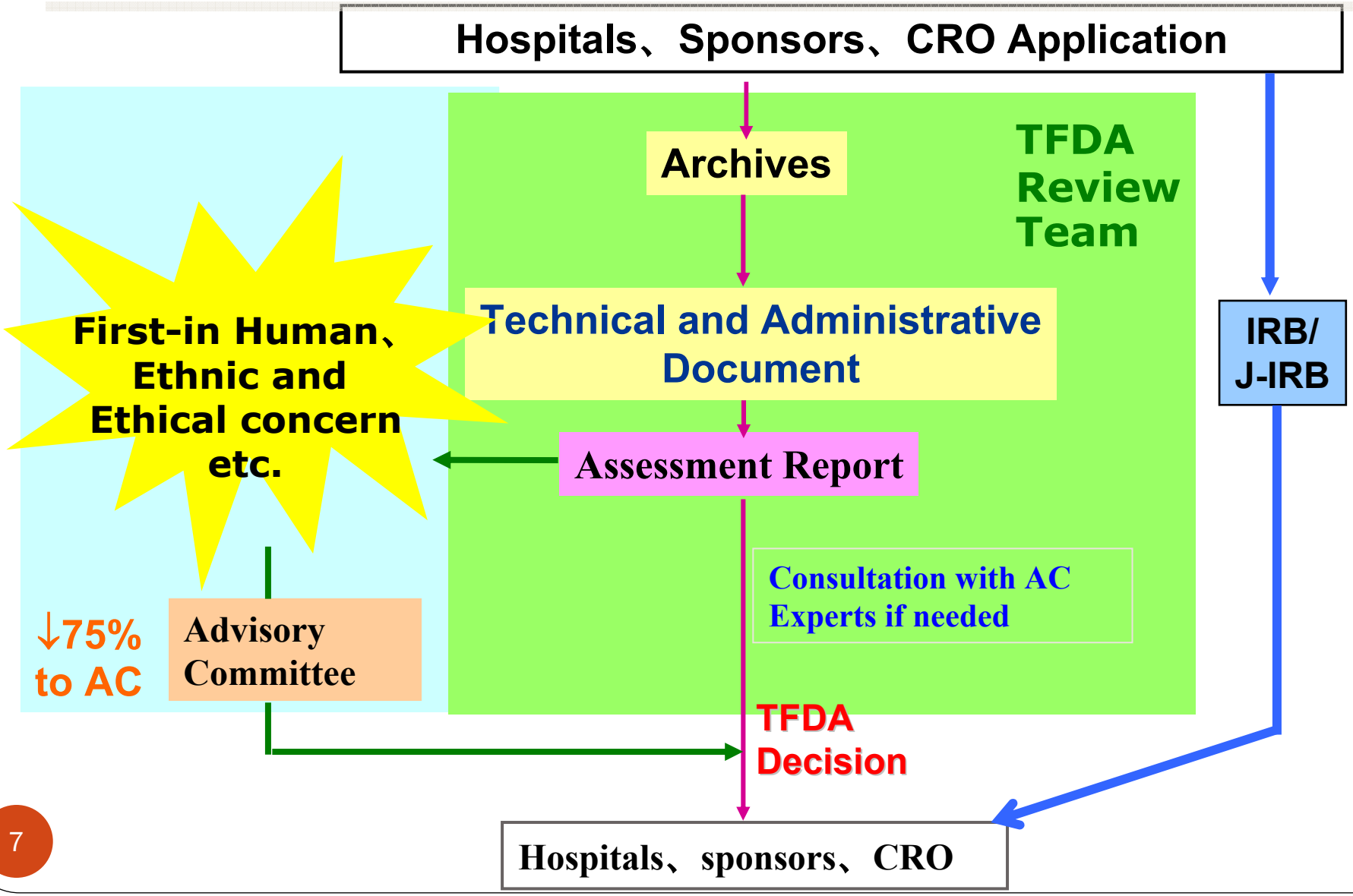
Pharmaceutical Regulation in Taiwan



GCP Laws/Regulations in Taiwan

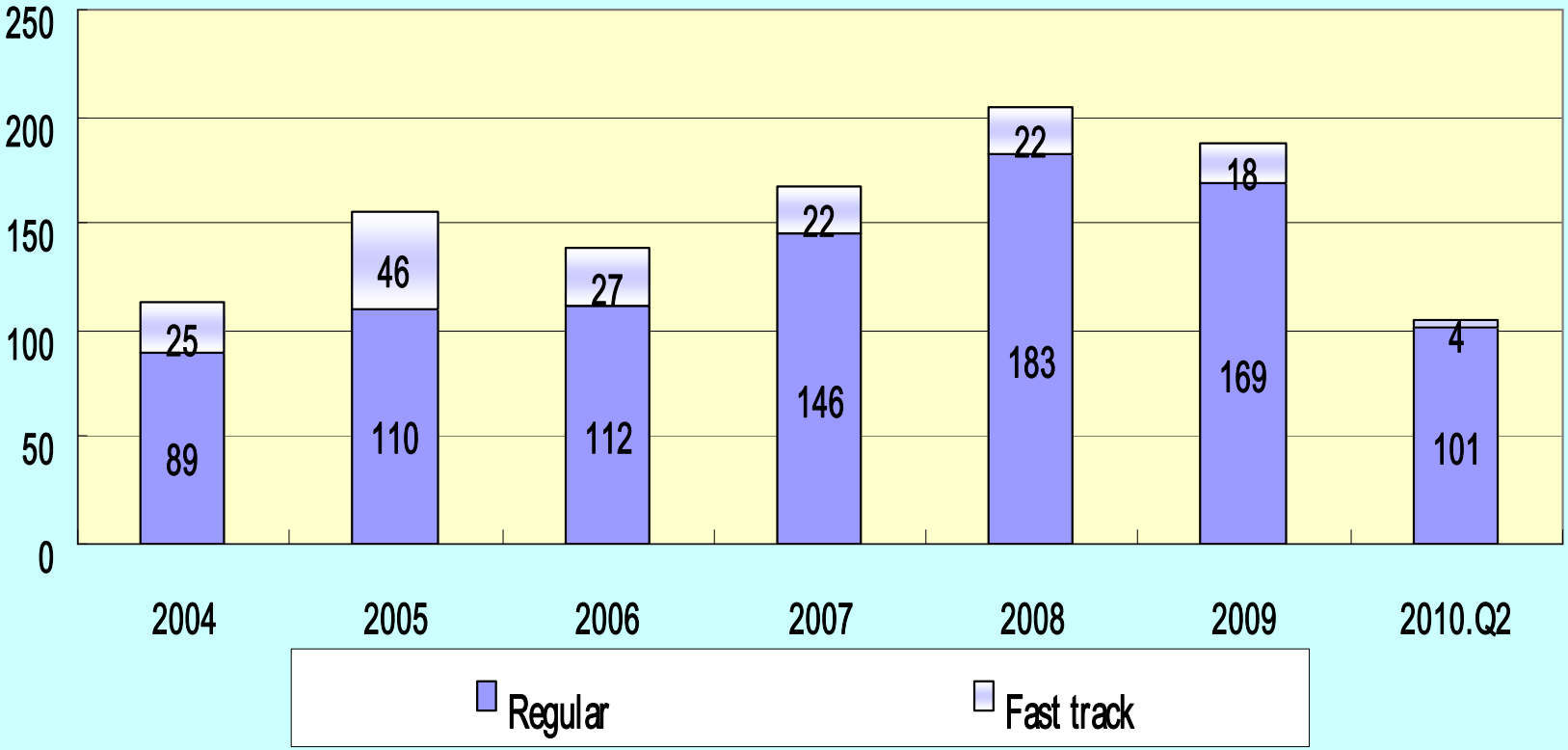
- Medical Care Act and Enforcement rules
- Pharmaceutical Affairs Act and Enforcement Rules
- Regulations for Good Clinical Practice
- Pharmaceutical Manufacturer Inspection Measures

Review Process for IND



IND Applications

(2004- 2010.06)

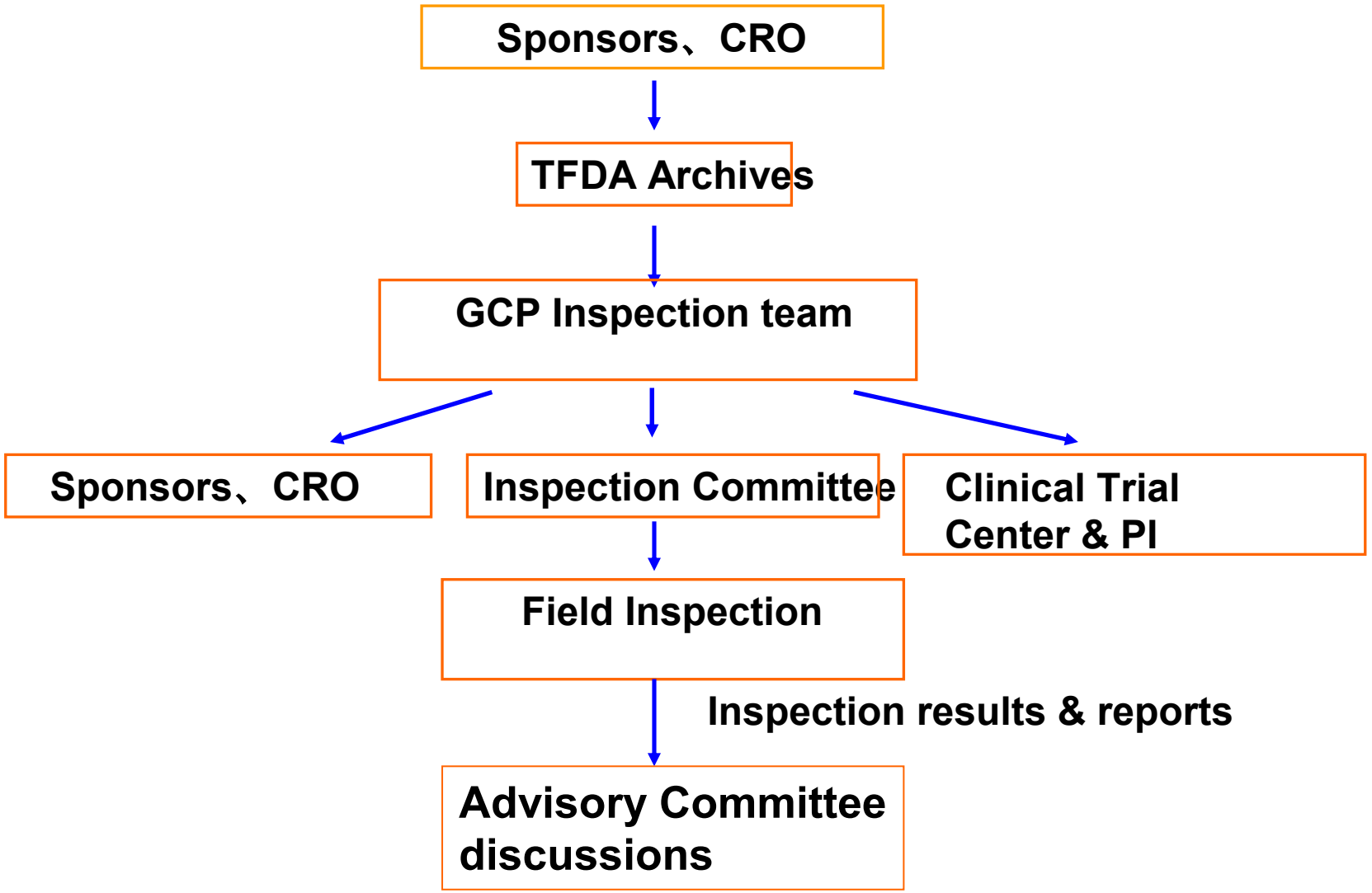


Distribution of Clinical Trial Applications (2005-2010.06)

	2005		2006		2007		2008		2009		2010.6	
	P	S	P	S	P	S	P	S	P	S	P	S
Phase I	14	26	12	20	10	18	11	14	18	19	10	12
Phase II	33	78	32	98	46	158	46	120	60	167	27	83
Phase III	69	242	86	300	106	391	132	527	95	407	55	251
Phase IV /others	4	5	3	4	6	14	16	21	14	19	13	22
Total	120	351	133	422	168	581	205	682	187	612	105	368

P: protocol S: site

Review process for Clinical Trial Report



Statistics for Clinical Trial Reports

Year	2002	2003	2004	2005	2006	2007	2008	2009
Inspection Cases	37	47	36	34	38	23	23	34 (10cases in review)
Disapproval Reports	4	4	5	2	2	0	4	3
Disapproval Rate	11%	9%	14%	6%	5.2%	0%	17.4 %	12.5% (3/24)

Clinical Trials Network in Taiwan

http://www.cde.org.tw/ct_taiwan/index.htm

International Cooperation

- Continuous international cooperation i.e. APEC (LSIF, ISTWG), ICH-GCG, DIA, etc.
- Bilateral Cooperation
  - Cross strait cooperation on new drug research and clinical trial
  - UK-Taiwan: Exchange Inspection & ADR report (2003)
  - Australia-Taiwan: Memorandum of Understanding (2010)
  - EU-Taiwan: Bilateral video-conference, Pre-notification of GCP, GMP inspection
  - US-Taiwan: Pre-notification of GCP, GMP inspection
  - Japan-Taiwan: Pre-notificaiton of GCP inspection


Thank You
for Your Attention
http://www.fda.gov.tw
Welcome to Taipei for the "2010 Good Review Practice Workshop on APEC LSIF" on Nov 3-5.

International Cooperation in the Regulation of Clinical Trials

David A. Lepay, M.D., Ph.D.
Senior Advisor for Clinical Science
U.S. Food and Drug Adminstration

September 7, 2010

U.S. FDA Perspectives and Approaches -1-

- OUS (Outside U.S.) Contributions to FDA Applications
  - Importance of the EU/EEA
  - Growing global contributions
- EMA/FDA Information Sharing and GCP Inspection Initiatives
  - The "pilot" and its status
  - What we (FDA) are learning from/about EMA

U.S. FDA Perspectives and Approaches -2-

- Global Learning and Potential Future Cooperation
  - FDA International Offices
    - (Europe, China, India, Latin America, Asia/Africa, Middle East…)
  - "Train-the-Trainers" initiative with OUS regulators
  - Ongoing international harmonization (e.g., PANDRH)
  - Stakeholder outreach (e.g., DIA; others)
  - Information from U.S. "sister" agencies
  - FDA marketing applications and international GCP inspections

Key Recommendations

- Continue/evaluate/refine current bilateral pilot initiatives (EMA/FDA)
- Train trainers (assess outcomes and seek long-term relationships)
- Overcome legal hurdles and increase opportunities for information-sharing
- Encourage global participation in regulatory forums
- Cross-reference each other's work (guidances/ procedures/ best practices) toward shared objectives
- Stress the need for documentable, verifiable performance

AFRICAN INITIATIVES FOR REGULATING CLINICAL TRIALS

(AVAREF AND PACTA)

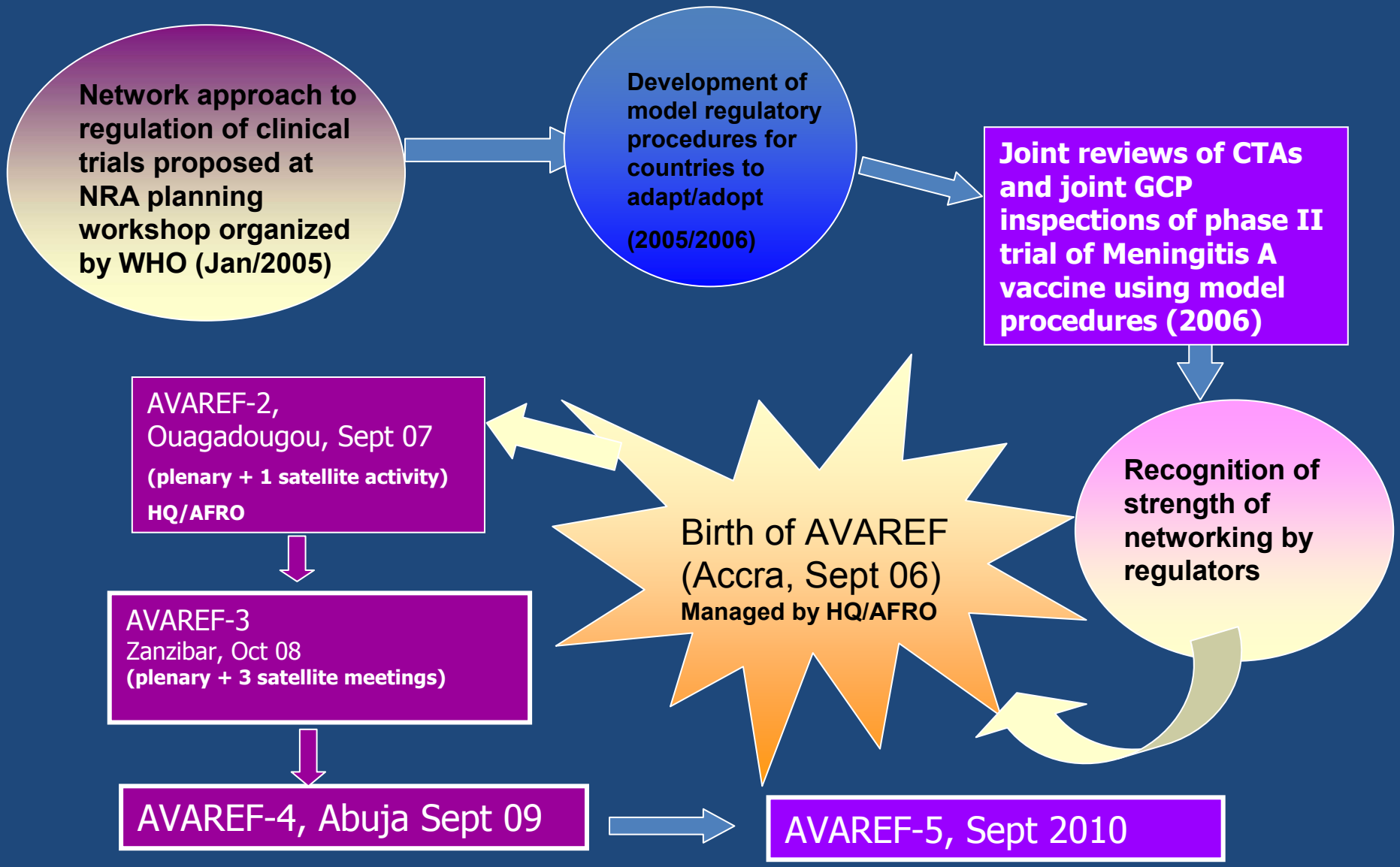
By AAron Sosola, MPH
Pharmacy, Medicines & Poisons Board-Malawi
7TH September, 2010

Background

Gaps in ethical and regulatory oversight of clinical trials in Africa identified by WHO :

- **Non-specific/lack of legal and regulatory framework for the oversight of clinical trials.**
- **Unclear mandates of ethics committees (ECs) and national regulatory authorities (NRAs)**
- **Wide disparities in the capacities of different countries**
- **Inadequate capacity to review clinical trial applications.**
- **Inadequate capacity to monitor CTs**
- **Inadequate documentation of processes**
- **Lack of collaboration between ECs and NRAs**
- **Inadequate information about activities of ECs and NRAs**

History of AVAREF

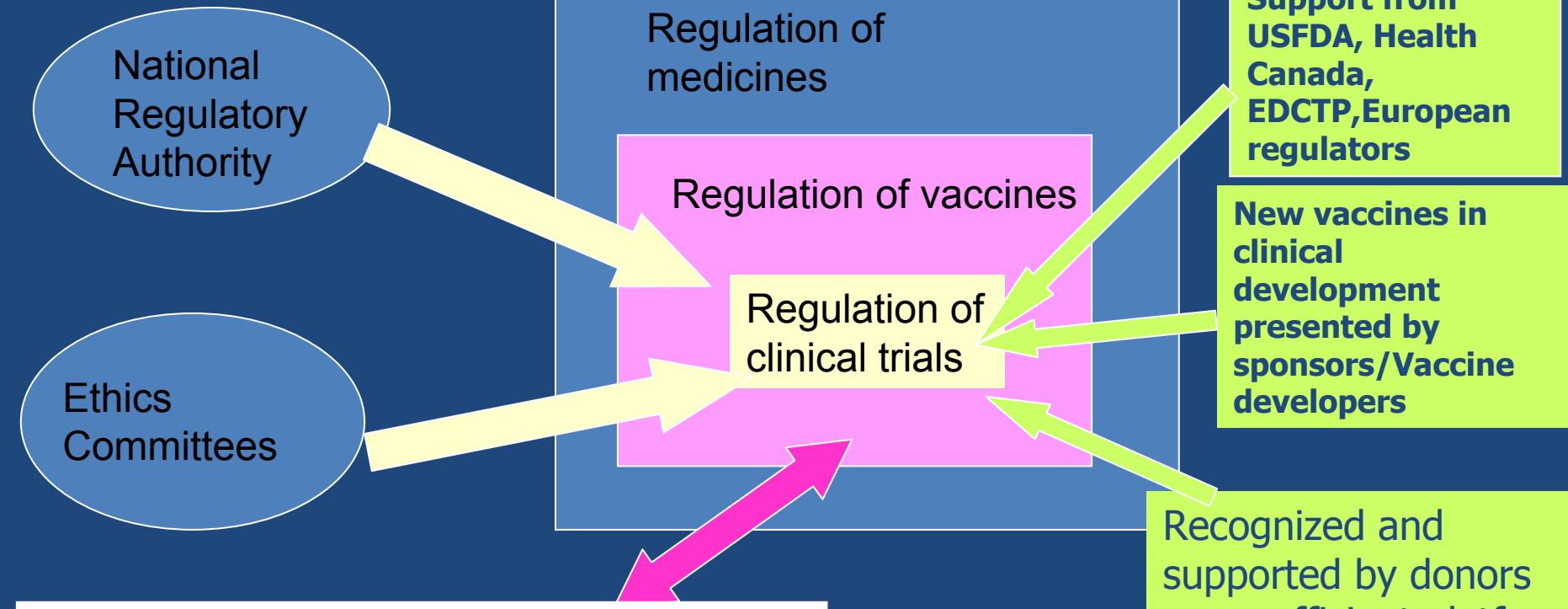


AVAREF-African Vaccine Regulatory Forum

An informal network approach to regulation of clinical trials in Africa

Representation: 19 countries target for CT of HIV, Malaria, TB, meningitis vaccines

Scope



Informal structure allows rapid and dynamic response as per needs identified

Currently working on formalization process

AVAREF: an effective initiative to stimulate progress towards regulatory harmonization of clinical trials

- Channels of communication among African regulators with regulators from developed countries have created confidence, strength and willingness to harmonize processes

- Model regulatory procedures developed and adopted by many African Countries

- Joint reviews and joint inspections conducted (Conjugate meningitis A and Malaria vaccines)

- Enthusiasm from countries for further developments:
  - integration of ethical review, regulation and registration of clinical trials (PACTA project)

  - development of African Common Clinical Trial Guidelines

Key required elements

This was achieved through:

a) Agreement from the manufacturer and sponsors as owners of the information.

b) A neutral partner to support WHO with funding and/or with negotiations with the owner of the information to ensure that the clinical trials would go through the highest possible level of regulatory oversight.

c) Consensus from the countries involved to review the application together, and to use the common report as the basis for their national decision.

d) Focal persons for the NRA and the EC in each participating country, to communicate with.

e) Experts that support the country regulators by sharing their knowledge and experience, but do not have decision-making roles or responsibilities.

Advantages of joint reviews (and inspections)

- Significantly more questions raised in joint reviews compared to individual country reviews thus providing a more comprehensive evaluation.
- Excellent learning experience by summing up findings from all countries plus expertise from advanced NRA
- Encourages harmonization of procedures and decision criteria
- Optimizes timeframes for review process
- Adds reliability to the clinical data resulting from those studies
- Sharing of knowledge and views.
- Evaluation in a timely manner without compromise in the quality of the review.

The Pan-African Clinical Trials Alliance (PACTA)

A strategy for ethical and regulatory oversight of vaccine clinical trials in Africa

Why the PACTA?

PACTA seeks to address these and many other gaps:

- Create a common platform for ECs, NRAs and the Clinical Trials Registry
- Will promote sharing, harmonization and strengthening of ECs and NRAs
- Create a common WHO primary clinical trial registry (Pan African Clinical Trial Registry (PACTR))
- Promote transparency, ensure safety of study participants, high quality clinical trial data and accelerated product development.

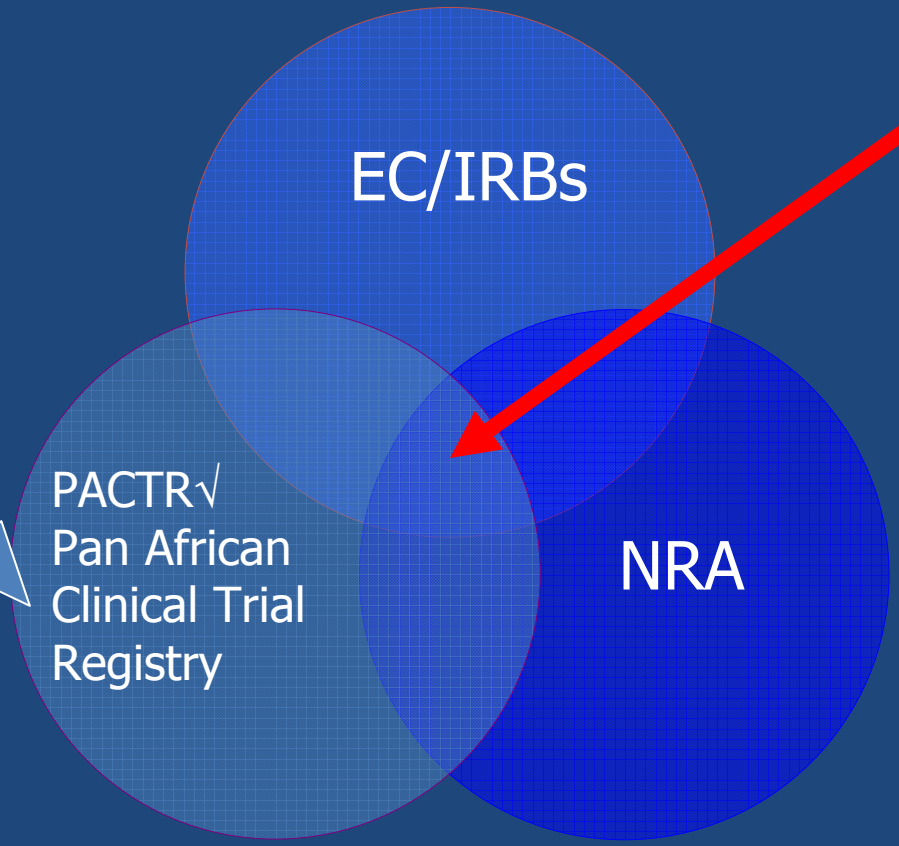
Ownership of PACTA

- Developed by task teams of African Vaccine Regulatory Forum (AVAREF)

- Botswana ,Burkina Faso, Ethiopia, Kenya, Gambia, Ghana, Gabon, Uganda, Tanzania, Mali, Malawi, Nigeria, South Africa, Senegal, Rwanda, Mozambique, Zambia, Zimbabwe

PACTA= Pan African Clinical Trials Alliance

ATM Registry



PACTA

Sharing

+

Strengthening

+

Harmonization

ATM=AIDS, TB & MALARIA REGISTRY

How Will PACTA Work?

- NRAs and ECs will share information about reviews and approval of CTAs
- NRAs will develop and use a common set of guidelines
- NRAs will share expertise
- Countries will have ownership of the strategy

Potential Benefits of PACTA

-Harmonized, common platform for submission and review of CTAs in Africa

-Common clinical trials registry, compliant with WHO requirements.

-Common platform for interaction between ECs and NRAs

-Common guidelines for GCP inspections of CTs

-Better definition of mandates for ECs and NRAs.

-Better ethical and regulatory oversight of CTs in Africa

NEW RECOMMENDATIONS FOR AVAREF-5

- The Pan-African Clinical Trials Alliance has become operational
- Funding for the rest of the PACTA strategy is being sought
- Revised concept paper to be presented to all Heads of Agencies and ECs to implement recommendations of the Ministers at the last RC meeting
- Pilot countries will include requirement of registration of trials submitted for authorization
- Harmonized guidelines for submission of CTA to be implemented

- New points will be proposed for primary registries to include proof of submission to NRAs and outcome of the review
- NRAs and ECs to agree on common set of data for national databases of CTs and "dialogue" with PACTR
- Pilot countries to use Heath Research Web (COHRED) and assess potential use as an information sharing platform
- Ongoing exchanges with EMA (CHMP and GCP inspection working groups)
- Discussions with FDA & Health Canada to facilitate expert support to countries target for CTs of products developed in US & Canada
- New opportunities for joint reviews of CTAs facilitated by neutral partners, under discussion
- Formulation of modules for legal framework for regulating Clinical Trials

International Cooperation in the Regulation of Clinical Trial Review and Inspection

Lucky S. Slamet
National Agency of Drug and Food Control
Republic of Indonesia

International Workshop on Draft Reflection Paper on Ethical and GCP Aspects of CT of Medicinal Products for Human Use conducted in Third Countries and Submitted in Marketing Authorization Applications to the EMA

London, 6-7 September 2010

Key Topics

- Key Issues on International Cooperation related to Regulation of CT Review and Inspection
- Lesson learned from International Cooperation on GCP Inspection
- Identification of Priorities, Opportunities and partners
- Examples of proposed Initiatives
- Action Plan

Key Issues on International Cooperation related to Regulation of CT Review and Inspection

- Regulatory Environment:
  - Approval for Study conduct (timeline)
  - License to import trial products and comparator
  - Permission to export Biological samples
- Local Ethics Committee Approval by sites
- Quality of CT Data Acceptable to advanced Countries (EU/US)

LESSON LEARNED FROM INT.COOP (1)

Indonesian Experiences as a Training Center

- Indonesia have been designated as one of the centers by WHO to conduct training since 2008.
- NADFC collaboration with the WHO Global Learning Oportunities / Vaccine Quality conducted three (3) WHO Global Learning Oportunities / Vaccine Quality.

The Training Course are:

1) Clinical Trial Authorization Course (CTA)
   - Jakarta, 27-31 July 2009 (16 participants from 9 countries)
   - Jakarta, 24–28 November 2008 (16 participants from 13 countries)

2) GCP Inspection Course
   - Jakarta, 22-26 March 2010 (13 participants from 7 countries)
   - Jakarta, 9 - 13 November 2009 (12 participants from 8 countries)

3) Evaluation of Clinical Data Course (ECD)
   Bali, 7 - 12 December, 2009 (14 participants from 9 countries)

The next course schedule :
- CTA Course : 25-29 October 2010
- EDC Course : 22-27 November 2010

LESSON LEARNED FROM INT.COOP (2)

Joint GCP Inspection Indonesia-South Africa (30 March – 3 April 2009)

- Preparation
  - planning, communication with the PI, announcement to the Site with a formal letter (SA team)
  - Review the study protocol to be inspected (Indonesia & SA Team)
  - Meeting between Indonesia team and SA Team
- On site
  - Opening meeting : Introduction, short interview with the PI about status of the trial
  - Review/verify the documentation, facilities and equipment
  - Closing meeting : summarize the findings, discussion with the Investigator Team
- Benefit :

  Sharing experience, compare the GCP inspection system, improvement the GCP inspection system, strengthening capacity building

Identification of Priorities, Opportunities and Partners (1)

6.1. Identification of Priorities

criteria need to be included

- Resource advantage/availability
  - Assessment of/assistance to country's internal resources :
    - Qualified investigators
    - Patients population i.e. large, diverse, therapy naïve
    - Clinical Research Infrastructure
    - IT Support
    - Connectivity—digital & facilities across countries

Identification of Priorities, Opportunities and Partners (2)

6.2. Identification of Opportunities and Partner

- to look for synergies
- To avoid duplication of effort and activities

- continuing improvement of collaboration as well as progress of collaboration

Establishment of contacts with the key initiatives need to be focus on:

- identify the contact person (Regulatory aspects; ethical standard etc) in each country
- Identify factors contributed to strengthening infrastructure and competence of Regulator
- Identify local NGO and CRO most experience in conducting CT in the country

Action Plan

Major Items should be included and are not in the paper:

GCP Inspection

ed same standard for categorization of GCP
ling.

uld be disseminate to NRA, Ethic
s sponsor for same interpretation

Regulatory Authorities

country
ial proposals

Ethical Committee

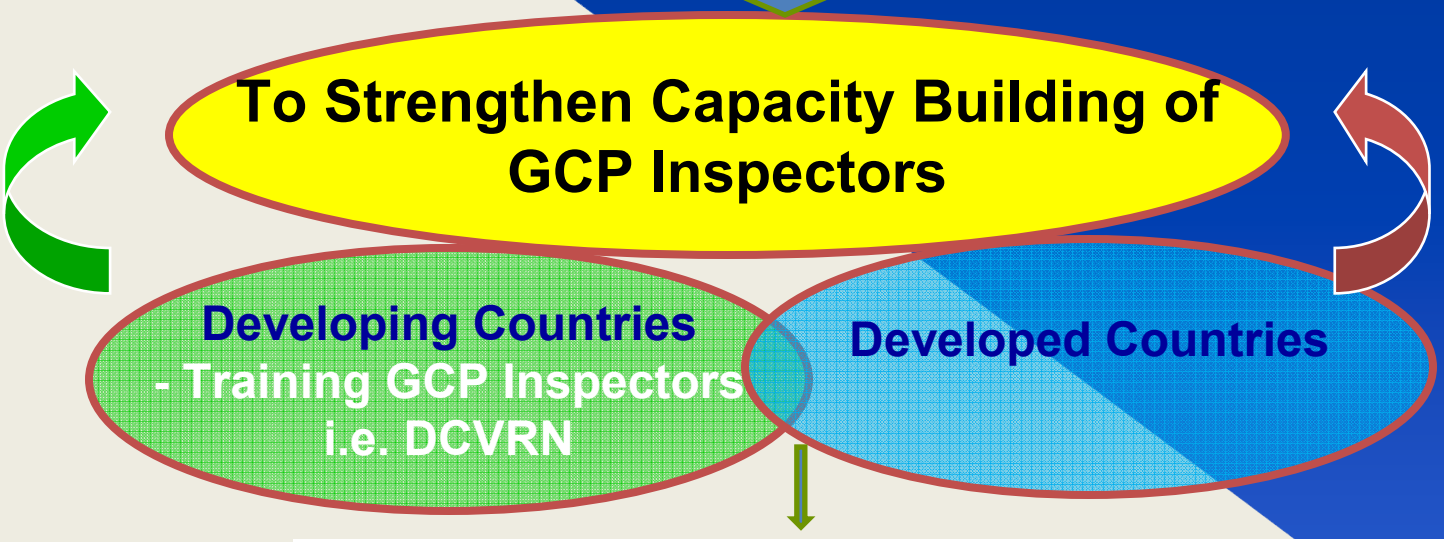
Investigator/Sponsor/CRO

ntation in

Example of Proposed Initiatives

Joint Inspection

ard for categorized of finding



- Update of GCP related information
-Share information with GCP Inspectors
- Conduct collaborative of GCP

Recommendation

Activity for Follow Up :

- Preparing Standard for Categorization GCP Inspection finding
- Sharing of data between various countries among Regulatory Authorities (RAs) and among Ethical Committees (ECs), as well as among RAs and ECs
- Robust review process for clinical trial proposals
- Sharing of experience related to clinical trial implementation in various country among investigator/sponsor/CRO

Thank You

VISIT INDONESIA

Bali

Bunaken – North Sulawesi

Mt. Bromo-East Java

Borobudur-Budha's Temple-Central Java

Prambanan-Hindu's Temple-Central Java

Agenzia Italiana del Farmaco

AIFA

International Workshop:

Draft reflection paper on ethical and legal aspects of CT conducted in third countries

Session 6: International cooperation in the regulation of CT

Regulatory Authorities perspective

Dr. Umberto Filibeck
Italian Medicine Agency
AIFA

6-7 September 2010 – EMA, Canary Wharf, London, UK

EMA Reflection Paper, Para 6.3.3
Long terms activities

The establishment of a "**Service**" linked with the international organizations, the EU Member States, institutions, third countries, NGOs (...) – to collect the following information for each developing country where a relevant number of CT are conducted:

1. *"The laws and regulations governing this field;*
2. *Information on National Regulatory Authorities, Ethics Committee and GCP Inspectorates;*
3. *Centers or Research Groups with experience on conducting trials according to the above mentioned ethical and GCP requirements, as shown by favourable reports from GCP inspectorates;*
4. *Models of initiatives implemented in the framework of international cooperation and information on obstacles encountered and their real efficacy".*

This could provide a useful support for implementing interventions that can be: more **targeted to the real needs**, more **selective** and **complementary** and defined on the basis of the efficacy results**.**

(EMA, Reflection paper)

Such a "**Service**" could be particularly useful for in the following contexts:

- to verify compliance to the principles of GCP for a certain clinical trial;
- to support a country through capacity building initiatives;
- to conduct clinical trials in developing countries;
- to provide advice on the preparation of regulations or procedures in this field.

(EMA, Reflection Paper)

Main objectives:

a. Establishment of contacts with the aim to create an international network of CT regulators;

b. Coordination of existing initiatives:
   1. <u>to avoid:</u>
      - unnecessary duplications;
      - initiatives with unfavourable results;
   2. <u>to encourage initiatives:</u>
      - with favourable results;
      - in identified neglected areas;

c. Achievement of high level of information from all countries where CT submitted to EU are performed.

European Service on Ethical, GCP and Regulatory Framework for CT in 3rd Countries (ESEthGCP in 3rd Countries)

Proposal of a model

Proposal: organization of the "Service"

a. **Coordination Centre**: EMA together with MS acting as Liaison Centers and EC, WHO and other entities;

Responsibilities:

1) lead the Service, by harmonizing MS Liaison Centers initiatives;

2) maintain strategic links with international and regional bodies;

3) co-funding of MS Liaison Centers initiatives.

b. Member States Liaison Centers

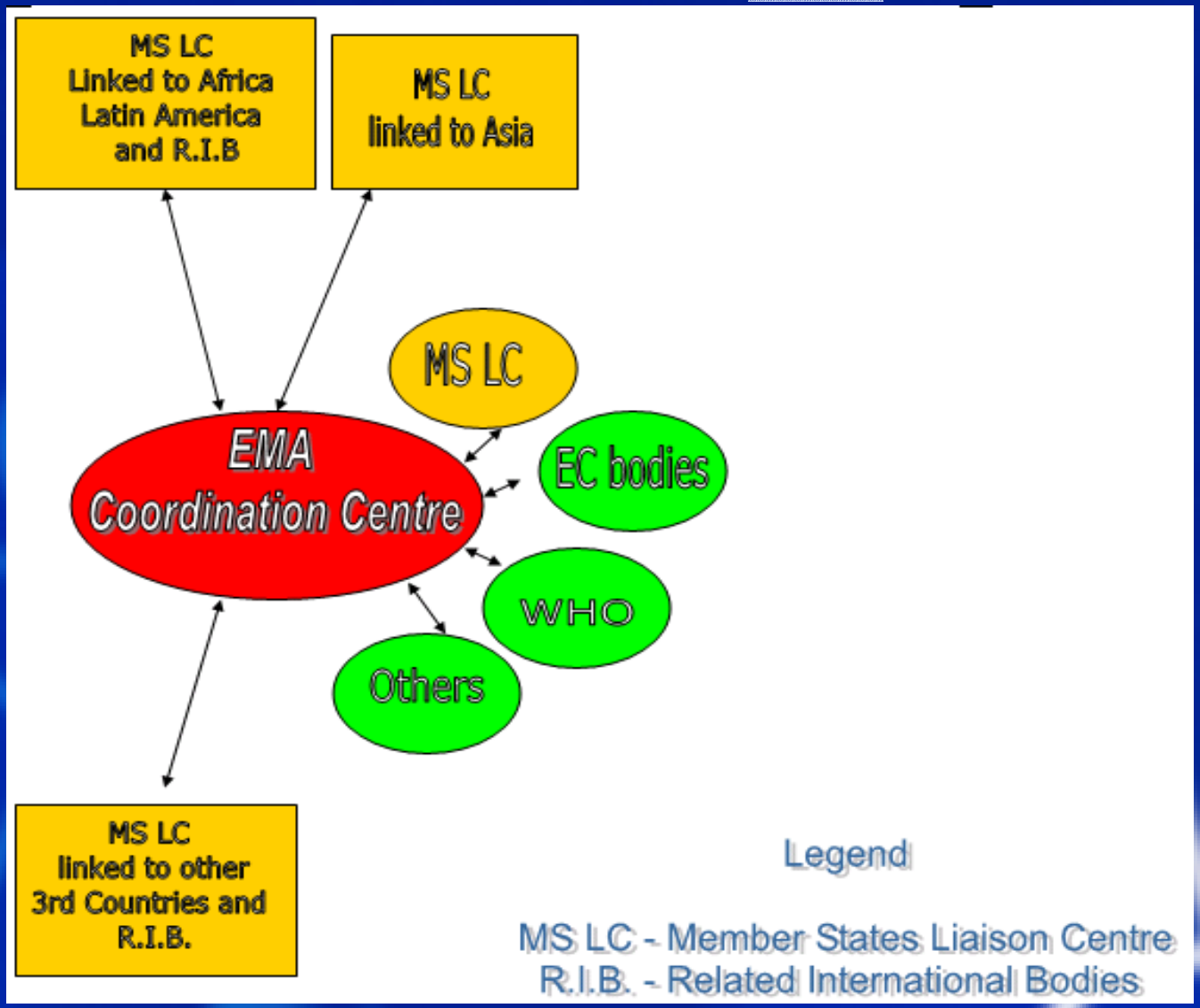
Identification: on voluntary basis

Responsibilities:

1) Connection with third Countries of a selected region and with International organizations and NGOs active in the same geographical region with the aim to:

- collect, evaluate and diffuse information;
- implement pilot courses;
- organize observed/joint inspections.

2) Co-funding of activities mentioned in point 1)


MS LC
Linked to Africa
Latin America
and R.I.B
MS LC
linked to Asia
MS LC
EMA
Coordination Centre
EC bodies
WHO
Others
MS LC
linked to other
3rd Countries and
R.I.B.
Legend
MS LC - Member States Liaison Centre
R.I.B. - Related International Bodies

Example

Key recommendations for the ***establishment of the "European Service on Ethical, GCP and Regulatory Framework for CTs in 3rd Countries"***
(ESEthGCP in 3rd Countries)

AIFA invites EMA to undertake measures aimed to the establishment of the Service, starting from 2011, and to identify:

- International bodies to connect to the Service EMA Coordination Centre;

- The fund-raising best modality to build the Service;

- MS ready to ensure their availability to act as Liaison Centers and related deadline, by specifying human and financial available resources and preferred geographical area and activities.

DCVRN
Considerations and Suggestions for EMA *Reflections* Paper

Developing Country Vaccine Regulators' Network

James A Southern

September 2010

EMA standpoint

- **DCs host clinical trials to support EMA MAA**
  - **These CTs may also support MAA in DCs.**
  - **Some DC NRAs have adequate control of CTs**
- **EMA has a regulatory interest in such trials.**

- **2008 Strategy Paper considered "Capacity Building" Proposed building a *"Network of Regulators"***
- *EMA will seek to build and extend its relationship with regulators in all parts of the world and with international organisations in order to achieve this*. **[EDCTP]**

Developing Countries & Clinical trials

- More than 20% of Clinical trials supporting MAAs in the EU have been conducted in 3rd countries, and more than half of these are in DCVRN member countries.

- The sponsors of CTs require that the data from clinical trials are of good quality, ethically conducted and acceptable to NRAs in all countries where MAA is made. *But sponsor support for NRAs is often unacceptable.*

- A neutral facilitator can support a DCVRN initiative to improve the quality of regulatory oversight in trials.

EMA Actions could include

- **A series of bi-lateral agreements with the NRA of each DC where CTs may be conducted.**
- **AND/OR**
- **An interaction between the EMA and various existing regulatory networks**
  - of which, the DCVRN is one

EMA-DCVRN Interaction

- **The remit of the DCVRN includes such interactions**
- **Possible development of a GUIDELINE (Code of Practice)**
  - for member NRAs and local Ethics Committees
  - enable appropriate interactions with trial sponsors, Investigators, and 1st country NRA
  - assessment of local strengths and weaknesses and mechanisms for requesting assistance from sponsor-country NRA

Features of a GUIDELINE

- DCVRN have considered a
  - "Certificate of GCP Compliance"
  - Issued by an NRA on completion of the CT Final Report
  - Would require recognition of NRA competence by other NRAs
- Such a guideline could be adapted for the NRA and/or REC of non-DCVRN countries if it was seen to be applicable.
- It could be advisable if such a Guideline was not exclusively related to the EMA.

DCVRN
Summary slide

- DCVRN could work with other Regulators [EMA] to develop a Code of Practice for regulatory oversight of clinical trials that covers vaccines and other medicines

- Potential Outcome could include a
  – Certificate of GCP –
  to accompany the clinical trial Final Report

- Mutual recognition of the CoP by reciprocal inspections

- Such Code of Practice may not be EMA specific

Ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries

Annelies den Boer, Wemos

London, 6-7 September 2010

General Remarks

- A very ambitious document.
- EMA takes responsibility for protection of rights of vulnerable trial participants.
- If properly implemented it will be a strong signal to those engaging in clinical trials that ethics should be taken seriously.

Practical application ethical standards

- Ethics committees: Many ethics committees do not meet requirements. Sponsors should provide more detailed information on composition of the ethics committee.
- Informed consent: People in low income countries are more vulnerable. Compliance with guidelines should be regarded with great caution.

Practical application ethical standards

- Fair compensation: trial related injury difficult to prove. Burden of proof with the sponsor.
- Vulnerable populations: justification in the protocol why a vulnerable group is included and how this study will benefit them.
- Placebo controlled trials: Helsinki is the standard.

Practical application ethical standards

Post trial treatment :

- EMA should set clear standards concerning duration of post trial treatment.
- Successful interventions should be made available to the wider community.

Marketing authorisation

- Pool of experts to advise CHMP should include independent representatives from low income countries.
- EMA should develop a check list based on a more detailed description of ethical aspects mentioned under section 3 of the reflection paper.

Non Compliance

Directive 2003/63/EC already states that clinical trials conducted outside the European Community will only be taken into account during the assessment of a drug application if they have been carried out in accordance with ethical principles such as the Declaration of Helsinki.

Recommendations

- Assessment of MAA should be done with an ethical checklist based on an ambitious interpretation of ethical guidelines addressing the fact that trial subjects in low income countries are vulnerable.
- Non compliance with ethical guidelines should have serious consequences such as refusal of an unethical trial in an MAA.

Stichting Onderzoek Multinationale Ondernemingen
Centre for Research on Multinational Corporations

EMA international Workshop
6-7 September 2010

Irene Schipper

Stichting Onderzoek Multinationale Ondernemingen
Centre for Research on Multinational Corporations

Practical application ethical standards

- **Agree with the selection** of ethical standards to clarify
- **Local stakeholders/experts** and **NGO's** need to be involved in further processes
- **More transparency** is needed

Stichting Onderzoek Multinationale Ondernemingen
Centre for Research on Multinational Corporations

Practical application ethical standards

More Transparency, examples

- Can we check possible conflicts of interests of members of ethics committees?
- Can we check the blank informed consent form?
- Can we check the ethical considerations made? The justifications? The provisions?
- Can we check where trials are conducted?
- Can we find all trials in public databases?

Stichting Onderzoek Multinationale Ondernemingen
Centre for Research on Multinational Corporations

Assessment issues MA phase not addressed

- Focus on pivotal trials
- No possibility to initiate GCP inspection by ‘outsiders’

Stichting Onderzoek Multinationale Ondernemingen
Centre for Research on Multinational Corporations

Key Recommendations SOMO

- Increase transparency

  - Include ethical considerations, justifications and provisions in the protocol, clinical trial registry database, public assessment reports, and clinical trial study reports and provide access to this information

  - Make trial registry in public databases compulsory
- Make it possible for anyone to initiate GCP inspection
- Involve local stakeholders and NGO's/research organisations in coming processes
- Development of ethical checklist

Draft Reflection paper on ethical and GCP aspects of clinical trials of medicinal products: A view from Latin America

Antonio Ugalde, Nuria Homedes
Salud y Farmacos and RELEM
London, September 6-7, 2010

Overall Comments

- Very comprehensive, detailed and well-crafted document

- Main Concerns:
  - Can it be implemented in LA?
  - How to balance the role of EMA and the sovereignty of countries

Premises to keep in mind

- The capacity of LA to conduct clinical trials varies by country but in general…
  - Patients tend to be recruited from the public sector → low SES, low levels of education. Vulnerable? May be. If so, is it just? can EMA accept it?
  - The actual implementation of the trial is often occurring in private sector center (some are ill-prepared to deal with complications, and regulatory agencies have limited control)

Premises to keep in mind (cont…)

- Informed consent is often “not informed” and may not be given “freely” (clinical trials may be the only means to access treatment, and it is often the attending physician who enrolls the patient)
- Regulatory authorities and ethics committees are doing very few inspections, when they occur they tend to focus on bureaucratic issues → little is known about patients’ compliance and quality of data collection
- Drugs tested in LA not always correspond to the priorities of the countries in which the drug is being tested

Premises to keep in mind (cont…)

- Ethics Committees (institutional or independent) are seldom independent and tend to be weak… National Ethics Committees appear to operate better, but not all countries have one
- Systems to report adverse effects and insurance policies to cover patients are ill-defined, often insufficient and the locus of responsibility is often unclear
- Clinical trial researchers have acquired significant levels of formal and informal power and influence governments and regulatory agencies

Premises to keep in mind (cont…)

- People (members of ethics committees, regulators, researchers) who dare to unveil unethical behaviors in the implementation of clinical trials are threatened and even removed from their posts
- The implementation of clinical trials is surrounded by secrecy: registries are not made public and in some cases inexistent or incomplete, no idea of number and characteristics of people participating in trials, researchers and ethics committees involved
- With the appearance of CROs the responsibility for the trials has been further fragmented

What can EMA do

- Changes in the ethical implementation of clinical trials in LA will only occur if EMA and FDA demand compliance with standards
- EMA can react to violations of ethical principles but must also strengthen the strategies to document violations (we agree with the document). Conducting inspections during marketing authorization phase is too little too late.
- In the case of LA, because of the formal and informal power of the researchers, the strategies to strengthen the countries' ability to monitor and ensure compliance with scientific and ethical standards should include civil society

What can EMA do

- Promote transparency in all aspects surrounding clinical trials →crucial step to ascertain how they are being implemented, who is participating in them, and build social control
- Support the development of national or at least regional ethics committees, and may be advisory boards for ECs
- Demand that the participation of vulnerable populations be drastically reduced and ensure that projects involving vulnerable populations develop interventions to ensure that informed consent is truly informed and uncoerced

What can EMA do

- Support the development and implementation of educational programs (communities and potential clinical trial participants) on clinical research, as a means of increasing social control and the ability of participants to consent
- Develop clinical trial observatories to collect information, ascertain compliance with ethical principles, and disseminate the results
- Develop systems to protect those who detect and unveil ethical violations of clinical trials

INTERNATIONAL WORKSHOP

DRAFT REFLECTION PAPER ON ETHICAL AND GCP ASPECTS OF CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR HUMAN USE CONDUCTED IN THIRD COUNTRIES

6-7 September 2010 – London, UK

Amit Sengupta

Health Action International

Peoples Health Movement

Balancing Risks and Benefits of Clinical Trials in Developing Countries

A Preliminary Interrogation of Praxis in India

Clinical Trials: Why India?

- Low costs (estimated as 60% lower than in developed countries)
- Relative high levels of technical expertise (and proficient in English!)
- Large population base which is largely "treatment-naive",
- Representing genetic diversity
- Populations at risk from diseases of poverty and underdevelopment as well as "lifestyle diseases"

Rapid Growth in Clinical Trials

- Amendment of Rules in January 2005 -- Principle of "Phase Lag" replaced by permission for Phase 2/3 trials for drugs discovered outside India to be conducted concurrently with international trials.
- Industry estimates: one in four clinical trials in the world conducted in India; turnover for the clinical trials "industry" expected to touch US$ 1.52 billion by 2010
- Registered ongoing trials exceeds 700 (in 2009) - up from around 250 just two years earlier, and likely to touch 1,000 in 2010
- 25-30% rise in no. of "clinical investigators"/year

(Doesn't entirely square up with data from EMA that trials in India account for a very small fraction (1.5%) total no of trial subjects as regards EU MAA)

Causes for Concern

Public Health lag

- ✓ Inadequate public health services creates environment that distorts process of recruitment and ability of benefits of trials to be available

Regulatory Lag

- ✓ Registration made compulsory only in 2009
- ✓ Inadequate staff strength to inspect and regulate
- ✓ Instances of Ethics Committee "shopping"

Capacity Lag

- ✓ Quality of investigators not uniform – demand for investigators outstrips availability

Ethical Lag

- ✓ Driven by CROs interested in promoting clinical trials as a commercial enterprise

Cause for Concern: Some Evidence

✓ Increasing deaths during clinical studies

- 132 in 2007,
- 288 in 2008
- 637 in 2009
- 462 till June 2010

(Source: June 2010, Ministry of Health)

Who Participates in Trials?
Motivation of Trial Subjects

- "looking for a cure" – 15%
- looking for "observed benefits" – 13%
- better treatment – 15%
- higher quality care – 15%
- free medical care – 10%
- doctor advised to enter trial – 15%
- receive money – 5%
- to advance scientific knowledge – 11%

- Investigator was primary physician – 76%
- Referred by primary care physician – 21%

Source: Study by CRO Excel Life Sciences quoted in Sandhya Srinivasan, Ethical concerns in clinical trials in India: an investigation, Centre for Studies in Ethics and Rights, Mumbai, India, February 2009

Who Conducts Trials?

Motivation of Institutions/ Investigators

Resource-starved public facilities

- 15 per cent of budgeted expenses paid to the institution by CRO
- Principal investigators get invited to all-expenses paid conferences abroad

Investigators in private hospitals

- Iinvestigator paid according to number of patients recruited between $1,500 and $3,000 per patient

Suggestions to Safeguard Interests of Patients

- Comprehensive five-year health insurance for all participating volunteers
- Sponsors must give viable bank guarantees as proof of sincerity in assuming obligation of compensation
- Similar socio-economic profile of trial subjects in EU and Third countries
- GCP Certification for Centres conducting Ethical Trials
- Negative list of CROs, Trial Sites (including Ethics Committee) and Investigators found guilty of violating norms/ with inadequate capacity
- All trials to be referred to Expert committee in Third Countries comprising of Reps. of EMA, Third Country FDA, and CSOs with capacity, eminent individuals
- Disclosure by EMA of list of trials in a Third Country that are for the purpose of MAA in the EU

- Need to develop Criteria to assess that treatment will be available to community
- Need to develop a concept document on role of CROs and SMOs

Thank You!

Patients' Perspectives

Kin Ping Tsang

- Chairman, Alliance for Patients' Mutual Help Organizations (APMHO), Hong Kong, China.
- Secretary, International Alliance of Patients Organizations (IAPO)

7 September, 2010

Patients' Perspective on Core Principle of Clinical Trials

- Patients support clinical trials on research and development for new drugs and therapies with the core principle that the interests of the human subjects are placed ahead of all other considerations e.g. science, economic, society and others.

Recommendations – Local Ethics Committee

- **Ethical Standards:**

  3rd countries must be equivalent to EU. To conduct clinical trials in 3rd countries must not because of concession or lower ethical standards.
- **Patients' Representation:**

  Sponsors have the obligation to include patients' representation in the local ethics committee.
- **Transparency of review process:**

  Local ethics committee has the obligation to disclose information to patients organizations and public as long as the issues are related with public interests.
- **Appeal mechanism:**

  To review by an international appeal board when patients organization objects the decisions made by local ethics committee.

Recommendations – Informed Consent

- **Patients Engagement:**

  Local ethics committee has the obligation to engage Patients organizations in drafting and writing up information sheet and consent.

- **Communication of Informed Consent:**

  To effectively communicate the information and consent to subjects of vulnerable population such as print and cognitive disabilities, healthcare illiteracies, etc. by clinical psychologist or qualified counseling experts.

Recommendations – Vulnerable Population

- **Inclusion of Vulnerable Population:**

  To include vulnerable population in clinical trials in 3rd countries should be the last option and must be proven that there is no other alternatives, the inclusion must be cautious and minimal.

Recommendations – Access to Treatment

- Sponsors have obligation to support participants to access to appropriate treatment at the end of the trial.

Key Recommendations

- Equivalent Ethical Standards
- Obligatory Inclusion of Patients' Representation
- Transparency of Review Process
- Appeal Mechanism for Patients Organizations
- Patients Engagement in Informed Consent
- Effective Communication of Information to Vulnerable Population
- Proof of No Alternatives before Include Vulnerable Population
- Support Subjects to Access to Appropriate Treatment after Trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Summary of keys points on the topic of the Draft Reflection Paper

International Workshop on acceptance of clinical trials – ethical and GCP aspects, 6-7 September 2010, EMA, London.

Maria Antonietta Antonelli, Compliance and Inspections, European Medicines Agency

- **Ethical principles are universal and not negotiable.**

- **Equivalent ethical and scientific standards should be applied everywhere in the world regardless of the current strengths or weaknesses of regulatory or other systems.**

- **It is not acceptable to create double standards for EU countries and non EU Countries.**

- **Participation in clinical research is crucial for the development of the framework for clinical trials research and of health care systems.**

- **The Guidance should not restrict access or availability of clinical trials in 3rd countries because of more stringent requirements than those requested in the EEA**

- **International cooperation is necessary to regulate international clinical trials effectively and efficiently**

- **Importance of establishing a framework for the sharing of information, knowledge and expertise, in each national regulatory authority.**

- **The international cooperation should include the implementation of systems for the control of clinical trials and the improvement of capacity building for Ethics Committees and regulatory Authorities according to their local needs.**

- **Ethics Committees play a key role in the verification that ethical standards are applied at the time that the trials are conducted.**
- **The quality of Ethics Committees can vary widely between and within countries.**
- **Needs for support**

  a. *capacity buildings of ECs;*

  b. *quality standards for the independence, operation , accreditation and audit of ECs*

  c. *mechanisms in place to ensure that these quality standards are adhered to, such as a national accreditation or audit system*

  d. *Development of expertise to support Ethics Committees addressing difficult ethical issues*

Needs to improve the transparency at different level

- ***Ethical consideration, justification and provision should be clearly described in the protocol and in the Clinical study report;***

- ***The assessment of the GCP ethical standards should be included in the European Public Assessment Report (EPAR)***

- **Assessment of an application should consider both scientific and ethical aspects**.

- **Needs to clarify which ethical standards the agency considers acceptable.**

- **Pool of experts to advise EMA/CHMP on ethical issues, including the perspectives of low income countries and patient's representatives**

- **EU Competent Authorities who have serious concerns about design or conduct of a clinical trial should in certain case refuse to consider data from studies where serious violation of ethical standards have occurred and should communicate their concerns to the National Regulatory Authority where the trial have been carried out.**

Please note that these are only some key points highlighted during the discussion of these two days.

THANK YOU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Where do we go from here?

International Workshop on acceptance of clinical trials – Ethical and GCP aspects, 6-7 September 2010, EMA, London.

Thomas Lönngren
EMA
Executive Director

Next steps

- Public consultation on draft reflection paper until 30 Sep 2010 – written submissions are requested.
- Summary report of workshop and slides to be published by end of Oct 2010
- Written submissions to the Consultation process to be published by end of 2010
- Draft reflection paper to be revised, reviewed, finalized and published - target mid 2011.
- Implementation of the practical actions set out, and further development of policy and processes where needed.

International Cooperation

- Continue to build partnerships – bilateral and multilateral

- Work with existing fora and build on these – international organizations, DCVRN, EDCTP, ICH regulators' forum etc

- Work together to develop a network for GCP

Capacity building

- Participation in research is crucial to the development of healthcare systems and of regulatory and ethical review processes.
- Continue to open our training opportunities to GCP inspectors and other experts from third countries
- Work with partners to develop capacity building tools and opportunities and to identify funding opportunities
- Use ongoing processes to help capacity building, e.g. inspections in local countries, article 58 assessments, to share expertise

Processes and expertise

- Enhance our processes of assessment and inspection.

- Work with stakeholders to improve and develop the information in protocols and clinical study reports addressing the care taken to protect trial participants.

- Ensure access to advice on ethical issues – expert group to advise EMA and its committees when needed.

Transparency

- Improve the content and consistency of EPARs
  - locations where trials are conducted,
  - the standards to which trials were conducted
  - discussion of particular concerns.
- Support continuing development of public clinical trial registries.
- Continuing, wider, development of EMA transparency policy.
- Continue to involve wide range of stakeholders in discussions.

Goals

Subjects/patients participating in trials are fully protected – wherever the trial takes places

Availability of safe and effective new medicines, as early as possible, with data relevant to all regions

Excellent open discussion.

Broad cross section of stakeholders and countries.

Wide ranging discussion – to which we have listened carefully

Thank you