



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency Perspective

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An agency of the European Union





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EU requirements for clinical trials conducted in support of marketing authorisation submitted to the EU

This presentation and the documents referred to relate to the conduct of trials required to support MAA in EU

Requirements apply:

- To all clinical trials that are included in a MAA submitted in the EU/EEA
 - regardless of the route (Centralised, Mutual Recognition, Decentralised)
 - regardless of the EU or third country involved (legislation does not differentiate developed, developing etc)
- Apply to the clinical trials included in a MAA
- There is no specific legal framework for review of a clinical trial dossier by an EU regulator before the conduct of the trial in a third country



The Dilemma.....

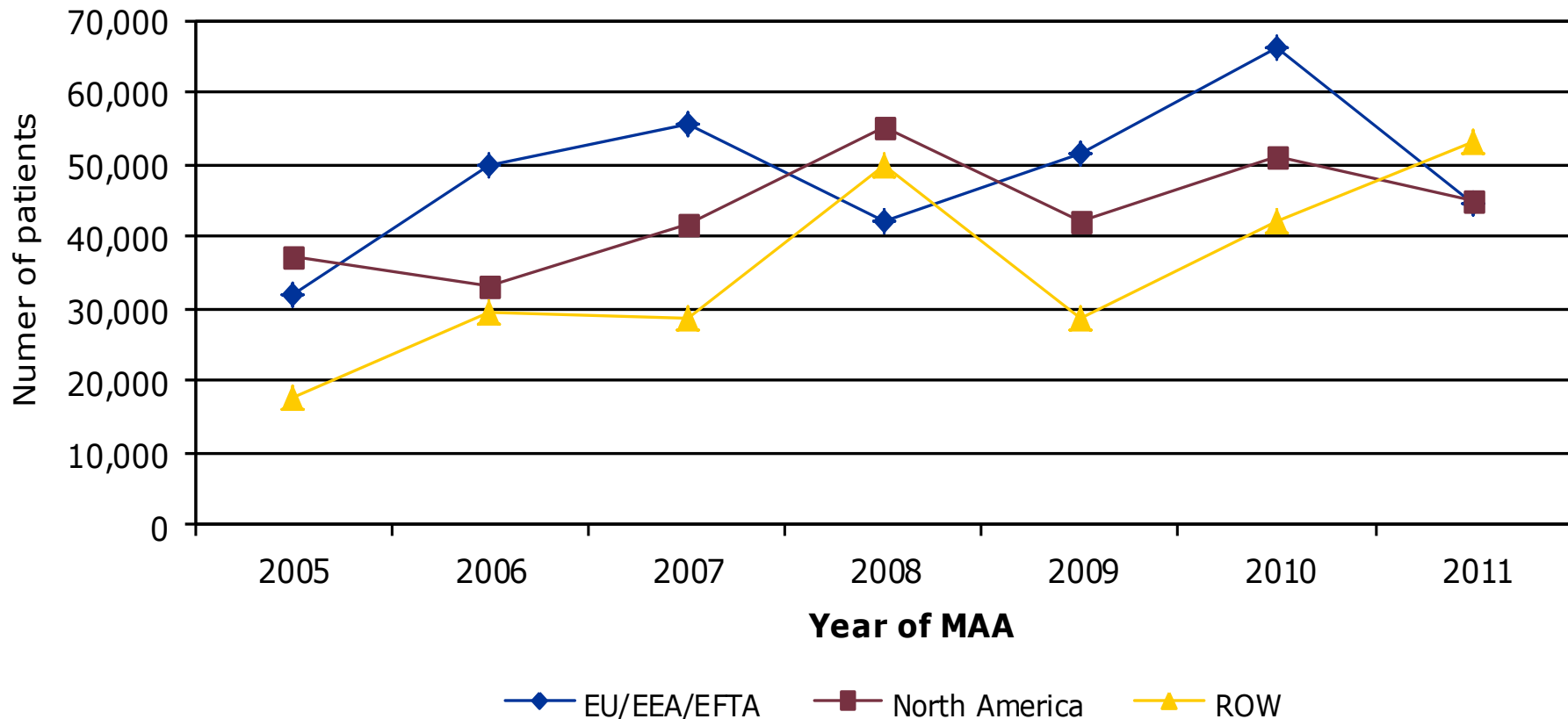
Between 2005 and 2011

897,891 Patients in pivotal trials

(38.11% in Europe, 34.05% in North America, 2.58% Africa, 9.36% Middle East/Asia Pacific, 4.44% CIS, 9.36 % Latin America, 2.1% other)

70,291 clinical trial sites in c. **106** countries

c. 485 new MAA applications plus line extensions etc,
265 GCP inspections



Number of patients in pivotal trials submitted in MAAs to the EMA per region and year. The data are shown as three “global regions” – EU/EEA/EFTA, North America and ROW (Rest of the World).



16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Released for Consultation	26 May 2010
End of consultation	30 September 2010
Agreed and Endorsement by CMD	14 June 2011
Agreed by EMA Working Group on Clinical Trials conducted outside of the EU/EEA	05 July 2011
Endorsement by CHMP	19 October 2011
Endorsement by EMA Management Board	15 December 2011
Endorsement by Heads of Medicines Agencies	24 February 2012
Date coming into effect	1 May 2012

Keywords	<i>Clinical trials, GCP, Marketing Authorisation Applications, EMA, EU, Ethics, conducted outside of the EU</i>
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Draft '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' Public consultation completed 30th September 2010.

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

<http://www.ema.europa.eu/Inspections/docs/71239709en.pdf>

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



Clarification of the practical application of ethical standards for clinical trials on medicinal products for human use in the context of the European Medicines Agency activities

- Local ethics committee and national regulatory authority oversight
- Information/Consent procedure
- Confidentiality
- Fair compensation for study related injury
- **Vulnerable populations**
- Choice of control - placebo and active comparator
- **Access to treatment post trial**
- Applicability of data to EEA population – addressed in other guidance



Vulnerable populations

Current DoH:

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.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.



Vulnerable populations

"The inclusion of vulnerable subjects in a clinical trial without the approval of the Ethics Committee and without implementation of the appropriate consent processes is a serious violation of ethical standards.

EU Regulatory Authorities should disregard data obtained in such an unethical manner, when submitted in support of a MAA."

- In this [clinical trials included in MAAs] context it is mainly vulnerability due to poverty, lack of access to adequate health care systems, lack of access to medicines.
- Need to ensure that vulnerable persons or groups are not exploited for the benefit of EU patients.
- At the same time there are the needs to consider the benefit to the patient of taking part in the study and the ethics of potentially turning them away simply because they fit one of the vulnerable categories.
- Denying access to research is also not a solution.
- Information on the populations included in clinical trials in a MAA and any particular concerns should be part of the European Public Assessment report.



Access to Treatment Post Trial

Current DoH

14. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

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



Access to Treatment Post Trial

- Access to innovative medicinal products varies widely.
- Differences mostly reflect ...theeconomic situation and social and health care systems of the country or region.
- Whether the medicinal product is likely to be available in the community or country should be considered by the sponsor, Ethics Committees and National Regulatory Authorities. New medicinal products should be intended for marketing in the countries or regions where the clinical trials are conducted.
- For the individual patient who participated in a clinical trial continued access to the product that has been identified as beneficial is crucial. It is recognized; however, that post trial access of patients to treatment or medical care provided by sponsor or investigator cannot substitute for shortcomings of national or regional health care systems.



Access to Treatment Post Trial

Transparency on matters of post trial access to treatment and medical care is paramount for clinical trials submitted to EMA in support of European MAA.

This information will be summarised in the European Public Assessment Report (EPAR).



Biobanks

Current Declaration of Helsinki

“25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.”



Biobanks

- Note for Guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (EMA/CHMP/ICH/437986/2006)
- Reflection Paper on pharmacogenomics samples testing, testing and data handling (EMA/CHMP/PGxWP/201914/2006)
- Reflection paper on pharmacogenomics in Oncology
- Large-scale study of populations may contribute significantly to science's understanding of the complex multi-factorial basis of disease and to improvements in prevention, detection, diagnosis, treatment and cure. Pharmacogenomics (PGx) offer a potential for better understanding the mechanisms of diseases and optimizing the development and use of medicinal products.
 - optimize the benefit/risk balance evaluation
 - provide focussed information as guidance to prescribers and patients.
 - may become a valuable tool in risk management and pharmacovigilance strategies.



Biobanks

- The use and exchange of human genetic material and the information derived from it, is not without some controversy. Within the scientific community, there is consensus that progress in understanding disease will depend on the establishment, harmonisation and broad use of human biobanks and genetic research databases.
- Human biobanks and genetic research databases which bring together and allow the sharing of human biological material and information derived from its analysis, are a key element of the scientific infrastructure underpinning such research.
- The potential of the Biotechnology can be developed only if data included in human biobanks are made available for research.
- The conditions under which the genomic data can be linked back to a subject's personal identifiers for any purpose, including the return of genomic data to the subject, should be described in research related documents, e.g. the informed consent document.
- Data protection and confidentiality have to be considered and ensured. In the EU the



Enhancement (Medical Enhancement)

Directive 2001/83/EC defines a medicinal product as:

“Medicinal product:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
- (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

EMA’s role is to review MAAs for medicines whose proposed function is to treat or prevent disease. The issue of “enhancement” is therefore out of the scope of EMA activities and therefore no comment is offered.



GOAL

- 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