United Nations
Interregional Crime and Justice
Research Institute

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

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

RECOMMENDATIONS OF EU PARLIAMENT EXPERT GROUP MEETING

"Ethics should become more of a priority issue when granting drugs EU marketing authorization. Political and financial support and commitment are needed to prioritize ethics throughout the European Union in a coordinated way."

"The latest version of the Declaration of Helsinki should be operationalized. Tools should be developed to better assess the ethical aspects of clinical trials when granting a drug marketing authorization. This process should be done in consultation with experts from low-income and developing countries."

"Clinical trials are increasingly being carried out on trial subjects in developing countries. In such countries, the end of a drug trial often also means the end of any treatment at all. Therefore, post-trial treatment arrangements are an especially important example of an aspect of the Declaration of Helsinki that needs to be operationalized."

EU REQUIREMENTS FOR CLINICAL TRIALS CONDUCTED IN THIRD COUNTRIES

Directive 2001/83/EC as amended by Directive 2004/27 - Whereas….(13) :

"… ethical requirements of Directive 2001/20/EC … to apply to all medicinal products authorised within the community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, *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*."

Article 6(1) of Regulation No (EC) 726/2004 and Article 8 (ib) of Directive 2001/83/EC as amended the MAA dossier to contain:

"A statement to the effect that *clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC*."

Section 4 of Introduction to "Annex I" - Directive 2003/63/EC :

"applicants shall take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use"

Section 8 of Introduction to "Annex I" - Directive 2003/63/EC:

"To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, 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."*

ACCEPTANCE OF THIRD COUNTRY TRIALS IN MA APPLICATIONS TO EU REGULATORY SYSTEM

- Ethical issues
- Data quality issues
- Applicability to EU population
- Applicability to EU medical practice

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

For the purpose of research, **three ethical principles** should be adhered to:

a) **respect for persons**,

b) **beneficence,**

c) **non-maleficence** and

d) **justice**, where respect for persons includes the respect for autonomy and the protection of dependent and vulnerable persons, beneficence/non- maleficence is defined as the ethical obligation to maximize benefits and to avoid or minimize harms, and justice is a fair distribution of the burdens and benefits of research

ETHICS COMMITTEE AND NATIONAL REGULATORY AUTHORITY OVERSIGHT

Regulatory action / action plan

Failure to submit a protocol to an **independent EC** is a **serious violation** of ethical standards.

EU Regulatory Authorities should disregard data obtained in a such unethical manner.

The applicant for a MAA should provide EU Regulatory Authorities with a **summary of Ethics Committee**, and **National Regulatory Authority approvals** of each clinical trial supporting the MAA.

This information should form part of the clinical study report in accordance with ICH E3.

EU Regulatory Authorities should identify **those studies that may give rise** to special **ethical concern**

Where clear serious concerns are identified the EU Regulatory Authorities should communicate these concerns to the National Regulatory Authority of the Country (ies) concerned.

The Sponsor ensuring that the clinical trial is reviewed by an appropriate EC should consider the opportunity to submit the clinical trial also to an **Ethics Committees** (either in an **EU or non EU Country**) that operates within an established regulatory framework with ethical standards equivalent to those applying in the EU.

Evidence of the mechanisms put in place **should be provided**.

INFORMATION/CONSENT PROCEDURE

Regulatory action / action plan

- **Failure to obtain** informed consent (and/or assent where applicable) is a **serious violation** of ethical standards. EU Regulatory Authorities should disregard data obtained in a such unethical manner
- The applicant for a MAA should provide EU drug regulatory authorities with a **summary of the consent processes used**
- EU Regulatory Authorities should **identify** those **studies that may give rise to special ethical concern** regarding the consent process

VULNERABLE POPULATIONS

The applicant for a MAA should provide drug regulatory authorities with an **adequate and appropriate justification** for inviting vulnerable individuals or groups to serve as research subjects

EU Regulatory Authorities should **identify those studies that may give rise to special ethical concern**

PLACEBO AND ACTIVE COMPARATOR

"In some circumstances it may be **acceptable** to use an **alternative comparator**, such as placebo or "no treatment"[*WHO (CIOMS) Guideline 11*], whilst taking into account that "the **rights, safety and wellbeing** of the trials subjects are the most important considerations and should prevail over the interests of science and society" [Paragraph 2.3 of ICH-E6; Directive 2005/28, art. 3.1]

- "**Economic [or logistical] reason** for the unavailability of an established effective intervention **cannot justify** a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study" [WHO (CIOMS) Guideline 11]

- EU Competent Authorities should **verify** that the study has been reviewed by the **ethics review committees** and that they have determined: whether the use of **placebo or other comparator is ethically acceptable in the context** of that trial; whether the **safety and rights** of the subjects have been fully **protected**

Regulatory action / action plan

- Sponsors should describe in detail in the protocol and in the clinical study report the **justification for the use of placebo** and/or choice of **active comparator** in accordance with the ethical principles referred to above.
- EU Regulatory Authorities will **identify** those **studies that may give rise to special ethical concern** regarding the use of placebo or other comparators
- Where it is determined that a study design was not acceptable in accordance with the aforementioned criteria, it should not be accepted in support of a MAA

ACCESS TO TREATMENT POST TRIAL

For the individual patient who participated in a clinical trial continued **access to the product that has been identified as beneficial is crucial.**

Paragraph 14 of the Declaration of Helsinki requires: 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 [Para.33 of Declaration of Helsinki (2008)]

Regulatory action / action plan

- The applicant for a MAA should provide EU Competent Authorities with a **description** of the situation of trial participants with regard to **post trial access to treatment**
- EU Regulatory Authorities should **identify those studies that may give rise to special ethical concern** regarding access to treatment post trial
- EU Regulatory Authorities will **summarize this information** in the Public Assessment report

Thank you for your attention!

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