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## **EMEA strategy paper: Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications.**

### **Introduction:**

The revisions to the pharmaceutical legislation which came into force in 2005 increased emphasis on the ethical standards required of clinical trials conducted in third countries and included in Marketing Authorisation Applications (MAAs) submitted in the EEA.<sup>1</sup> There is growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organisational standpoint (including GCP compliance) and about the available framework for the supervision of these trials.

The number of clinical trials conducted, and of patients recruited into clinical trials, in countries outside of the “traditional” Western European and North American research areas has been increasing for a number of years.

EMEA has been actively tracking the geographic origins of patients included in pivotal trials submitted in MAAs to the centralised procedure. Approximately one quarter of patients recruited in pivotal trials submitted between 2005 and 2008 were recruited in countries in Latin America, Asia, Commonwealth of Independent States members and Africa.

Information is required in each MAA regarding the location of conduct and ethical standards applied in respect of clinical trials conducted in third countries. A system of routine GCP inspection is in place since 2006. Two key factors in selecting sites and studies for routine inspection are the presence of vulnerable populations (including children) and of investigator sites in developing countries. Both the review process and inspection programme are being expanded.

The EMEA Work Programmes for 2008 and 2009 set out a number of actions relating to clinical trials conducted in third countries. These actions include verification, at the time of the evaluation of the marketing authorization application, that trials carried out in third countries have been conducted in accordance with the required GCP and ethical standards. There should be greater transparency of this process, and its outcome, which should be described in the EPAR (European Public Assessment Report). The work programme foresees increased GCP inspection including further extension of the GCP policy on increasing numbers of routine inspections as part of the need for greater supervision of the conduct and ethical standards of clinical trials performed outside the EEA.

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<sup>1</sup> The Directive 2001/83/EC, as amended, states, in recital 13: “(13) There is a need to provide for the ethical requirements of Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 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 to apply to all medicinal products authorized 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.”

These activities need to be further developed and expanded and this requires a plan of action extending beyond 2008. The strategy set out in this paper will be translated into an itemised action plan set out over three years.

The key strategic areas to be addressed are set out as follows, building on the legal provisions, current activities to implement these and the 2008-2010 Work Programmes.

Whilst this paper is focused on third country trials many of the actions that arise (e.g. transparency in EPARs, increased training and awareness on ethical issues etc.) will have relevance for all clinical trials that form part of marketing authorization applications.

### **Three year plan of activities:**

The activities of the EMEA will address the process of clinical development not only at the time of Marketing Authorisation Application (by which time the pre-authorisation clinical trials have mostly been completed) but at earlier stages before and during the conduct of the clinical trials.

The activities proposed need to encompass all areas of EMEA activity with impact on clinical trials starting with the early activities such as Scientific Advice, Orphan Designation and Paediatric Investigation Plan and continuing through the finalisation of opinions on initial MAAs and clinical trials conducted post-authorisation.

This approach will therefore cover:

- Recommendations for the development of new medicinal products/conduct of clinical trials
- Orphan designation
- Protocol assistance/scientific advice
- Paediatric Investigation Plan
- Pre-submission phase
- MAA assessment (both initial submission, and variations/line extensions)
- Post authorisation clinical trials
- Inspection (before, during or after the MAA)

Action areas to be addressed within the scope of EMEA's responsibilities, and in the context of other initiatives being undertaken by the European Regulatory Network and the European Commission, include:

- Planning and development:
  - Clarify the practical application of ethical standards for clinical trials
  - Consider the issues driving the recruitment of subjects in third countries
  - Review the actions available in response to non-compliance, and establish a policy
  - Ensure links, with other initiatives taken by the EEA Member States in this area, in consultation with the European Commission DG Enterprise and the Heads of Medicines Agencies.
- Practical application
  - Further training and awareness of EMEA, experts and Marketing Authorisation Holders/sponsors
  - Submission, validation, assessment and inspection
  - Transparency, including improvement of EPAR content and consistency
  - Contribution to capacity building with developing countries in cooperation with Member States and European Commission initiatives.