EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency response to the European Commission's "ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC" launched in October 2009.

1 Introduction:

The European Medicines Agency (the Agency) welcomes the initiative of the European Commission in launching the assessment of the functioning of the clinical trials directive.

The Agency has a number of activities that are set out in the Directive 2001/20/EC and its implementing texts (e.g. in relation to EudraCT, EudraVigilance and inspection). In addition many of the Agency's activities are closely related to the conduct or outcome of clinical trials.

Medicinal products fall within the scope of activities of the Agency and of the NCAs (National Competent Authorities) at different points throughout their lifecycle. The Agency has worked closely with the European Commission and the National Competent Authorities of the Member States to assist in the implementation of the clinical trial Directive, and to support the increasingly close communication and partnership within the European Regulatory Network on clinical trial related issues.

The development of new medicinal products and of the underlying basic and translational research required to bring these products to the patients who need them are key elements of European research policy. The Agency supports a healthy research environment which is essential to the future well-being of EU patients and to the development of Europe as a key location for biomedical research and pharmaceutical development.

The Agency supports enhancement of the European Research Area for the development of medicines by the provision of a single point of application and assessment of each clinical trial, resulting in one authorisation valid throughout the Community. The assessment and authorisation of each clinical trial application could be local or central depending on the characteristics of the investigational medicinal product and of the clinical trial.

A coherent regulatory process that can assist the development of products from their inception, through scientific advice, first in human trials, and full clinical development is an important element in enhancing the European research environment. The concept of a "living license" with development of the data set both pre and post authorisation, greater use of post authorisation trials and the wider interests in these datasets need to be taken into account.

There is a need to introduce a clear, risk-based approach so that trials of well characterised products are simpler and quicker to initiate, and require lesser degrees of regulatory supervision, whilst trials of new, less well known products can be given the resource they require and merit. Simplification and streamlining of the process, at EU and national level are essential to these objectives.

Recommendations are provided below under the headings of the consultation document.

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KEY ISSUE N°1 TO BE ADDRESSED: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

Proposal for a single European IMPD (Investigational Medicinal Product Dossier) and clinical trial application:

Sponsors have called for a single point, in the EU, of application for clinical trials and hence a single application dossier to competent authority(ies) and ethics committee(s).

Currently the IMPD is compiled and updated with each clinical trial application, to each Member State, to which are added the clinical trial protocol and a number of other documents. The IMPD exists separately from Scientific Advice, Paediatric Investigation Plans, Orphan status applications and ultimately the Marketing Authorisation Application and any post-authorisation activity. Applications to competent authorities and to ethics committees are made separately per member state but most of the information is common to these applications.

It is proposed that a single European IMPD be opened for each new active substance, from the time of its first contact with the regulatory system in the EU. EU IMPDs would also be put in place for active substances/medicinal products which already have marketing authorisations, wherever new clinical trials commence with those products:

- The EU IMPD holder would be the sponsor-developer of the new active substance (and continuing to be held by the MAH (Marketing Authorisation Holder) post-marketing authorisation).
- Additional simple IMPDs, post-marketing authorisation, for research uses would be held by sponsors who are not the innovator (e.g. academic researchers, generic companies etc), cross referring to the marketing authorisation.
- Development of an electronic CTD (Common Technical Dossier)-like structure for the IMPD.

Each new clinical trial application, to both competent authority(ies) and ethics committee(s), would be made once, via a central point, and linked to the relevant EU IMPD. The EU IMPD would:

- support the review, authorisation, amendment and supervision of the individual clinical trials
- support a revised approach to a public clinical trial registry, but that public registry would have a separate status, whilst using common information sources, and standards (where applicable), (see separate section on clinical trial registry).

KEY ISSUE N°2 TO BE ADDRESSED: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

Safety reporting:

The processes for safety reporting from clinical trials and the review of safety information would benefit from a clear and fully harmonised legal basis for:

- the use of EudraVigilance as the EU database for electronic SUSAR reporting by sponsors and analysis by EU regulators,
- the population of the EudraVigilance Medicinal Product Dictionary,
- a single process for the evaluation of each Annual Safety Report, avoiding multiple submissions
- a mechanism for the evaluation of safety information, in particular expedited reports, on behalf of the ethics committees.

In this aspect the Commission's attention is drawn to the response from the EudraVigilance Expert Working Group to this public consultation (Doc. Ref. EMA/764025/2009).

KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

Risk based approach to clinical trial supervision and conduct:

There has been much discussion about the requirements applying to commercial and non-commercial clinical trials and in particular about the impact of the requirements on the feasibility of non-commercial trials. Common standards can be applied but with much greater differentiation between trials of novel, unlicensed products and those of products with a marketing authorisation. Research would benefit from greater clarity regarding the differing requirements at different stages of product development and knowledge, and with respect to the complexity of the trial and to its potential impact on the trial subjects.

There is a need for clear guidance on the practical implementation of standards in relation to the size and complexity of the trial design, the degree of knowledge of the IMP and the risk to the trial subjects, the latter with consideration to their potential benefit and the severity of their disease.

Support to academic research:

In addition to a clear risk based approach to the supervision and conduct of clinical trials, improved infrastructure to support research in Europe could be established. This might include greater support for the establishment of EU research networks (networks for Paediatric Research and for Pharmaco-epidemiological Research have already been foreseen and work on these has commenced). A common framework for training, certification/accreditation of sites and investigators, and other parties (e.g. CROs, central laboratories..) involved in clinical trials could be set up.

Legal frameworks and processes are needed in order to simplify the initiation of trials by academic sponsors, and in particular research on medicinal products which have a marketing authorisation.

It is recommended that the conduct of clinical trials by consortia or networks of investigators/institutions be facilitated; such networks often include sites and institutions outside the EU as well as within the EU and may be funded/sponsored by non-EU bodies (public or private).

Provisions relating to key elements of liability and insurance/indemnity would be needed to facilitate the conduct of clinical trials by academic organisations and the formation of consortia to support multistate research in the EU and collaboration with international sponsors, such as the US NIH, seeking to place trials in the EU.

KEY ISSUE N°4 TO BE ADDRESSED: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

Research in emergency situations:

Research in emergency situations is important and an ethical need. The Agency welcomes initiatives to clarify the requirements for such trials.

KEY ISSUE N°5 TO BE ADDRESSED: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Clinical trials conducted in third countries:

The Commission's attention is drawn to the Reflection paper on acceptance of third country clinical trials in Marketing Authorisation Applications to the centralised procedure which is currently being drafted by the Agency's ad hoc working group on this topic. It is expected that the paper will be published for consultation in the first half of 2010. It will include considerations on ethics, scientific guidance and advice, marketing authorisation application assessment and inspection and on international collaboration.

A process analogous to that of article 58 of Regulation No (EC) 726/2004 could be established for review of clinical trials to be conducted in developing countries. Such a process could have strong links to capacity building and involve the local country competent authority and ethics committee. Clinical

trials could be proposed to this route by WHO, EDCTP and other nominated international or regional organisations, or directly by the sponsors, or local national authority.

A certification process (analogous to the Certificates of Medicinal Products (CPPs) issued for marketed products) could be established to facilitate local third country oversight of trials that have also been authorised in the EU, this could be linked to a supplementary assessment to take into account local issues in the third country.

A platform for a global GCP network (inspection, standards, assessment, ethics review, capacity building, information sharing) could be established in collaboration with WHO, and international partners.

Clinical trial registry and EudraCT:

In conjunction with the EU IMPD process suggested above the scope of EudraCT to act as a clinical trial registry could be widened. The registry could become a public registry of clinical trials conducted in the EU (including trials not otherwise within the scope of the clinical trial legislation per se), in order to provide a service to EU researchers. The data entry could be made by sponsors, and registration extended to clinical trials conducted in third countries.