European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 November 2005
Doc. Ref. EMEA/CHMP/GTWP/203821/2005

COMMITTEE FOR THE MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

Draft

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE NON-CLINICAL STUDIES PRIOR TO CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

AGREED BY GENE THERAPY WORKING PARTY	6 OCTOBER 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	17 NOVEMBER 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	28 FEBRUARY 2006

Comments should be provided to Denisa de Chiara (Email: Denisa.dechiara@emea.eu.int) (Fax +44 20 7418 8613) by 28 February 2006.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8613
E-mail: mail@emea.eu.int http://www.emea.eu.int

1. INTRODUCTION

Gene therapy medicinal products (GTMPs) have been developed in the recent years with the aim of treatment or prevention of a variety of human diseases or, in some cases marking cells for *in-vivo* diagnostic purposes.

There is a variety of different GTMP types including plasmid DNA, vectors and genetically modified cells. By nature, GTMPs pose specific safety issues. In order to protect patients to which GTMPs will be administered, these issues should be addressed prior to clinical use.

GTMPs are medicinal products which fall under the definition of Art. 3 of Regulation (EC) No 726/2004 and point 1 of the Annex of this same Regulation i.e. medicinal products developed by means of biotechnological processes and for which a marketing authorisation can only be granted by the Community in accordance with the provisions of Regulation (EC) No 726/2004.

Furthermore, GTMPs are defined in Annex I, Part IV, to Directive 2001/83/EC, as amended.

Directive 2001/20/EC, relating to the implementation of good clinical practice in the conduct of clinical trials of medicinal products for human use, has harmonised the national laws regarding the start and supervision of clinical trials by laying down the requirement for clinical trial approval in Member States and by setting the timing for the evaluation procedures, which are to be detailed in each Member State. The directive requires that written approval is given before a clinical trial with GTMP may start (Art. 9).

2. PROBLEM STATEMENT

Clinical trials with GTMPs have been carried out for many years now in the EU with many types of GTMPs. No GTMP has yet been authorised for human use in the Community. A number of GTMPs have been designated as Orphan Medicinal Products.

Directive 2001/20/EC (Clinical Trial Directive) lies down that clinical trial approval is the responsibility of each Member State. In the case of multinational clinical trials for a particular GTMP, a separate authorisation procedure will have to be carried out in each Member State in which a clinical trial is intended to be carried out.

When using a GTMP for treating an orphan disease, a multinational trial may be required to collect a sufficient number of patients. Although Member State competent authorities are not required by the Clinical Trial Directive to adopt a harmonised approach in the evaluation process, it seems highly desirable that a harmonised approach be taken for European multinational trials and also for trials that are carried out in more than one Member State. Since, at the end of clinical development, a marketing authorisation application will be submitted through the centralised procedure, a harmonised approach will facilitate clinical development processes in the EU.

Guidance has been provided to GTMP marketing authorisation applicants in the EU since 1994; the most recent revision of which is the Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99).

In addition, the ICH M3 (M) Note for Guidance on nonclinical safety studies for the conduct of human trials for pharmaceuticals was adopted in 2000 with the aim of harmonising international standards of non-clinical safety studies needed to support human clinical trials.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Before the implementation of Directive 2001/20/EC, clinical trials were regulated based on the national laws. Some Member States had National authorisation procedures in place, others had not. Due to the relatively recent implementation of Directive 2001/20/EC, the extent of experience of applicants and Member States with respect to its application is variable.

In Art. 9 of Directive 2001/20/EC, it is stated that the Commission, in consultation with Member States, will publish detailed guidance on the content of clinical trial applications.

The Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) contains information on requirements for product quality, preclinical and human pharmacology and pharmacokinetics studies. Although chapter 5 describes preclinical

pharmacological-toxicological studies, it lacks a specific discussion of what studies are needed before first use in humans or what can be postponed to a later clinical development phase.

The ICH M3 (M) covers development of conventional medicinal products and is intended to provide general guidance on toxicity, tolerability, safety pharmacology and pharmacokinetics studies to support the conduct of clinical trials for conventional medicinal products. It recognises that the paradigm described for safety evaluation may not be always appropriate or relevant for new types of therapeutics (see section 1.3).

In the case of GTMP, the type and extent of pharmacological-toxicological data needed for an appropriate risk-benefit evaluation will depend on the product type and construct, its proposed clinical use, the duration of treatment, the target population. Some issues, especially those specific to GTMPs are of particular importance, such as germ line transmission, biodistribution, insertional oncogenesis, target tissue specific expression and duration, induction of immune responses and potential efficacy.

A detailed description of the non-clinical requirements for the first use in humans of GTMP is needed. The non-clinical requirements needed to progress clinical development (phases II and III) are also undefined. General scientific requirements specifically for GTMP as defined in Annex I to Directive 2001/83/EC, as amended, would allow a harmonised approach between Member States. This would also help future applications for marketing authorisation for GTMPs.

4. RECOMMENDATION

Taking the general guidance given by ICH M3 (M) as a basis, development of a European guideline on the non-clinical requirements prior to clinical use of GTMP is recommended. A guideline is a sufficiently flexible document to accommodate the fast-pace scientific progress in the field.

5. TIMETABLE

It is anticipated that a draft guideline will be available 9-12 months after adoption of the concept paper and will be released for 6 months external consultation, before finalisation within further 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The guideline development will be lead by the GTWP in collaboration with SWP and in consultation with external parties.

A joint drafting group will be appointed with members of the GTWP and the SWP. Drafting work will be done primarily by email. It is anticipated that at least two meetings of the drafting group in 2005/2006 will be needed before the draft is presented to the GTWP and SWP.

GTWP and SWP will discuss draft versions at their regular meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline will give applicants and National Competent Authorities guidance on the non-clinical assessment of GTMP. Such a harmonised approach will contribute to protect European patients and to safely foster the development of GTMP use in EU. It will also streamline the clinical development and facilitate the future evaluation through the centralised procedure.

8. INTERESTED PARTIES

EMEA: GTWP, SWP of the CHMP.

External consultation: European Society for Toxicology, European Society for Pharmacology, European Society for Gene Therapy, EFPIA.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Regulation (EC) No 726/2004
- Directive 2001/20/EC
- Annex I, part IV of Directive 2001/83/EC, as amended.

- Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)
- ICH M3 (M) Note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals