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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUESTIONS AND ANSWERS ON GENE THERAPY

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ABBREVIATIONS USED IN THIS DOCUMENT

BWP:	Biologics Working Party
CAT:	Committee for Advanced Therapies
CHMP:	Committee for Medicinal Products for Human Use
EC:	European Commission
EMEA / EMA / Agency:	European Medicines Agency
EU:	European Union
FDA:	Food and Drug Administration
GMO:	Genetically modified organism
GTMP:	Gene therapy medicinal product
GTWP:	Gene Therapy Working Party
ICH:	International Conferences on Harmonisation
IMPD:	Investigational Medicinal Product Dossier
Ph. Eur:	European Pharmacopoeia
SWP:	Safety Working Party
VHP:	Voluntary Harmonisation Procedure
WHO:	World Health Organisation

INTRODUCTION

This Q&A document is developed and maintained by the Agency's CHMP Gene Therapy Working Party in collaboration with other relevant Working Parties and with the Committee for Advanced Therapies (CAT). A number of questions that have been brought to the attention of the GTWP by different stakeholders, on matters related to the development of gene therapy medicinal products, are addressed.

It provides harmonized position on issues that can be subject to different interpretation or require clarification, typically arising from discussions during briefing meetings with stakeholders.

If a question is not addressed in this document, the stakeholders are encouraged to contact the Agency for further information (the document will be updated regularly). Additional questions can be sent to the GTWPsecretariat@ema.europa.eu, for further consideration.

Please note that this document has been produced to provide clarification and/or additional information, and should be read in conjunction with the GTWP guidelines and other relevant guideline and guidance documents.

1. GENERAL QUESTIONS

1.1 What current European Medicines Agency guidelines are available related to how Gene Therapy based products are developed? Also, how can sponsors give feedback to the Agency GTWP on the current guidelines and their usefulness and make suggestions for improvements or additional guidelines for such products?

All guidelines, reflection papers and concept papers (including those not yet finalized but under public consultation) currently available for gene therapy can be found at: http://www.ema.europa.eu/htms/human/humanguidelines/multidiscipline.htm (under gene therapy).

Some of the guidelines are directed to the marketing authorization stage, whereas some include also guidance related to earlier stages of development.

Draft guidelines are available for anyone to comment at the above website. The draft guidelines are circulated for comments to all major stakeholders and company sponsors who have visited GTWP for briefing meetings (by the Medical Information Sector at the Agency). Everyone is encouraged to feedback their comments on the draft guidelines through the recommended route. If sponsors have ideas or suggestions for additional Guidelines these should be sent to the GTWP at GTWPsecretariat@ema.europa.eu .

1.2 What is the role and place of the European Pharmacopeia (Ph. Eur.) General Chapter on Gene Transfer Medicinal Products for Human Use?

The General Chapter 5.14. of the European Pharmacopoeia on *Gene transfer medicinal products for human use* contains an introduction stating that alternative approaches to those described in the chapter may be possible if authorized, as it was felt that the field is still under development and a more flexible set of requirements was needed. In any case, the recommendations included in General Chapter 5.14 should be taken into account during development and any deviations should be justified at the time of marketing authorization application.

The document "Status of EMEA scientific guidelines and Ph. Eur. monographs and chapters in the regulatory framework applicable to medicinal products" (http://www.ema.europa.eu/pdfs/human/hmpc/4237108en.pdf) explains the relationship between the Ph. Eur. and the Agency's guidelines.

1.3 What guidance and practical activities exist to support consistency and harmonisation of the assessment of the Investigational Medicinal Product Dossier (IMPD) for gene therapy IMPs?

The evaluation of clinical trial applications for gene therapy Investigational Medicinal Products presents special challenges due to the novel nature of these products and the limited expertise available. The development of a guideline on chemical and pharmaceutical quality documentation concerning biological IMP in clinical trials is ongoing and may contribute to harmonise requirements of suitable quality standards for gene therapy IMPs. In addition, the Guideline on the Non-clinical Studies Required before First Clinical Use of Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/125459/2006) describes harmonized non-clinical requirements for the early clinical development phase.

Furthermore, a harmonisation procedure for the assessment of multinational clinical trial applications has now been set up by the Clinical Trials Facilitation Group of the Head of Medicines Agencies, before the initial phase of the national process, and on a voluntary basis. Further information can be found in the Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications (http://www.hma.eu/uploads/media/VHP_public_CBB_22_Dec_08___hk_jan12.pdf).

2. SCIENTIFIC QUESTIONS RELATED TO GENE THERAPY

2.1 QUALITY

2.1.1 What are the requirements to establish comparability during product development?

Comparability requirements are discussed in the relevant ICH and Agency's guidelines such as the Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03). Please refer to http://www.ema.europa.eu/htms/human/humanguidelines/biologicals.htm for information. Additionally, a document on regulatory reflections on gene therapy product changes during development is under preparation by the GTWP. This paper would consider the impact of particular changes to the characteristics of the gene therapy product and reflects on the experience gained so far using specific examples. Most probably a case by case evaluation will be required as it will depend on the stage of development, the nature of the change and the significance of the data obtained after the change has been introduced. For more specific advice regarding proposed manufacturing changes and the required comparability data, the Applicant may consider seeking the Agency's or national Scientific Advice. In addition, informal discussions with the GTWP during a briefing meeting may guide the sponsor in the development of a robust comparability strategy, at an early stage of development.

2.1.2 Is there any specific requirement for full sequencing of the vector as a part of product characterization for gene transfer medicinal products?

General requirements for product characterization can be found in the Note for Guidance on the Quality, Pre-clinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99). More specific requirements for different types of gene therapy medicinal products, including sequencing of the vector, can be found in the Ph. Eur. - General Chapter 5.14 on *Gene transfer medicinal products for human use*. In general, full sequencing is required at some stage of production (e.g. at the level of the master or working stocks or at the end of production) but, most probably, final requirements will be decided on a case by case approach.

2.1.3 For vaccines and other biological products, general (WHO host cell DNA limit) acceptance criteria are set by the authorities as to how much residual host cell DNA may be in the product. Is this requirement also acceptable for Gene therapy products? Is there any specific guidance on the amount and/or size of the DNA fragments?

In our opinion, depending on which vector you are producing, it is often not possible to get the host cell DNA levels reduced to limits that are acceptable for vaccines. Although recommendations for

other biological products can be considered as an initial reference, at this time it would be best to judge host cell DNA content on a case by case basis. DNA levels should be as low as possible and the acceptance criteria established by the manufacturer should be justified. In any case this parameter should be considered in the benefit/risk relationship for every particular product and indication.

2.1.4 Is the presence of an antibiotic resistance gene as selection marker in a plasmid acceptable?

In accordance with the Ph. Eur. (General Chapter 5.14 on *Gene transfer medicinal products for human use*) and the Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99), the presence of an antibiotic resistance marker in a plasmid administered in vivo is not recommended. The presence of antibiotic resistance gene should be justified. Nevertheless, a risk assessment should be conducted and a final decision on whether or not the presence of a particular marker gene is accepted will be part of the final benefit/risk assessment of the product.

2.1.5 In October 2008, the FDA published draft guidance on requirements for potency tests for gene and cell therapy products. Does the European Medicines Agency plan to publish additional guidance on potency tests for gene therapy medicinal products?

The Agency's CHMP in association with relevant working parties have already included guidance on potency testing for gene therapy medicinal products in scientific guidelines. Most notable is section 2.5.2 of the Note for Guidance on the Quality, Pre-clinical and clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99), which came into force in 2001. The relevant sections of the 'Guideline on Potency Testing of Cell-Based Immunotherapy Medicinal Products for the Treatment of Cancer', which came into effect in 2007, are also of interest.

The Agency has a policy of continually updating its guidance to take into account advances in science and regulatory affairs. Since the first above-mentioned guideline has entered into force for a number of years, an update of its contents can be expected to be published for consultation in the near future.

2.2 NON-CLINICAL

2.2.1 Is there guidance in relation to tag sequences and their use in Gene Therapy Products?

If tag sequences are to be used in any construct then their presence and function must be fully justified and be part of the risk analysis. Also, when a tag sequence is included in a particular construct, it is expected that safety data be generated on the construct which includes the sequence, and that any studies are performed in line with the published guidelines. It is expected that any effects of the tag sequence on gene expression and toxicity be investigated fully and reported appropriately - see also the Note for Guidance on the Quality, Pre-clinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99).

The tag sequences should not have oncogenic or other pathogenic potentials.

2.3 ENVIRONMENTAL RISK ASSESSMENT, SHEDDING

2.3.1 Viral Shedding has been addressed under ICH - what are the next steps?

The ICH Gene Therapy Discussion Group has finalized Considerations on the General principles to Address Virus and Vector Shedding in July 2009. The document is now posted on the ICH and Agency's website. As presented on ICH website, a proposal for development of an ICH guideline on Virus and Gene Therapy Vector Shedding and Transmission has now been agreed (see ICH M6 concept paper - http://www.ich.org/cache/compo/276-254-1.html).

2.3.2 What are the GMO environmental requirements for approval of clinical trials and marketing authorisations in the EU?

For the approval of clinical trials, the GMO environmental aspects are evaluated by the National Competent Authorities and requirements may be different from country to country. In many countries the information must be submitted in local language. The National Competent Authority of the country where the trial is planned should be contacted for information regarding the necessary level of detail and required forms to be completed for approval of the trial.

For the approval of a marketing authorisation for a GMO product, the following Agency's guidelines should be followed:

- Guideline on Environmental Risk Assessments for Medicinal Products Containing, or Consisting of, Genetically Modified Organisms (EMEA/CHMP/473191/06),

- Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/125491/2006). The information provided in this guideline may also be helpful for the preparation of an application for approval of a clinical trial.

Further useful information is provided in:

- Directive 2001/18/EC on the Deliberate Release in to the Environment of Genetically Modified Organisms,

- Directive 98/81/EC amending Directive 90/219/EEC on the Contained Use of Genetically Modified Micro-Organisms.

- Directive 2000/54/EC on the Protection of Workers from Risks related to Exposure to Biological Agents at Work.

- Analysis of the Applicability of the Contained use Legislation for Clinical Trials. http://ec.europa.eu/environment/biotechnology/pdf/clinical_trial_study_report.pdf