European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE REVISION OF THE NOTE FOR GUIDANCE ON THE QUALITY, PRE-CLINICAL AND CLINICAL ASPECTS OF GENE TRANSFER MEDICINAL PRODUCTS

DISCUSSED BY GTWP / BWP / SWP / CPWP	September / October 09
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END OF CONSULTATION (DEADLINE FOR COMMENTS)	31st March 10

The proposed guideline will replace the Note for Guidance reference CPMP/BWP/3088/99.

Comments should be provided using this template to GTWPsecretariat@ema.europa.eu

KEYWORDS	*Advanced Therapy Medicinal Product, Gene Therapy Medicinal Product, Viral Vector, Oncolytic Virus, Bacterial Vector, Genetically Modified Cell, Quality, Non-clinical, Clinical*

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1. INTRODUCTION

This Concept Paper proposes a revision of the Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99) that came into effect in 2001. The revision of the Note for Guidance, Guideline according to the new terminology, will address the issues identified from clinical experience and provision of Scientific Advice on gene therapy medicinal products and will lay down detailed and updated requirements for the quality, non-clinical and clinical aspects of gene therapy medicinal products. The revised Guideline will refer to a number of recently developed scientific guidelines and will comply with Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products and the Commission Directive 2009/120/EC amending of the Annex I Part IV of Directive 2001/83/EC.

2. PROBLEM STATEMENT

Gene therapy involves state-of-the-art science and technology and is a rapidly developing field. Significant progress in the field of gene therapy was likewise highlighted in Regulation (EC) No. 1394/2007 on advanced therapy medicinal products. Since the adoption of the Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99), important issues have emerged during the CHMP provision of Scientific Advice and the MAA assessments for new gene therapy medicinal products. Some of the identified issues are not covered by the current version of Note for Guidance. The Gene Therapy Working Party (GTWP) aims at updating and refining the current Note for Guidance in line with the revised definition of gene therapy medicinal products, the amended Annex I Part IV of Directive 2001/83/EC and reflecting the significant development of the field of gene therapy.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Since the adoption of the current Note for Guidance in 2001, considerable advances have been made in the field of gene therapy, including the development of a wider spectrum of delivery vectors and clinical trials involving patients suffering from various diseases. It is noteworthy that significant modifications, e.g. self-complimentary or integration-deficient machinery, have been introduced to the conventional vectors such as AAV, adeno-, retro- and lentiviral vectors to improve vector safety. In addition, a number of new viruses and oncolytic viruses such as Epstein-Barr virus, Semliki, Sendai and Vesicular Stomatitis viruses have been adapted as delivery vectors for gene therapy. A novel class of vectors have been generated from bacteria and bacteriophage, e.g. Lactococcus, Listeria, Saccharomyces, Salmonella and Streptococcus for cancer therapy. With the progress of genome mapping projects, a number of chromosome-based vectors, e.g. iBAC, S/MAR and transposon vectors have been introduced to facilitate gene transfer. Many of these new delivery vectors have entered clinical trials. Issues specific to the emerged vectors may need to be referred in the revised NfG while being further addressed in individual reflection papers or guidelines.

Significant developments in gene therapy also include the advances in combined therapies with chemotherapy, recombinant proteins, medical devices and physical methods such as ultrasound, imaging and gene guns. Molecular profiling of patients and the use of biomarkers before and after treatment become increasingly beneficial and popular, topics for which specific issues related to gene therapy may need to be addressed. Complex issues associated with these therapies are likewise not covered in the current version of Note for Guidance. Issues related to the application of delivery vectors in stem cell therapy, to either facilitate a therapeutic function or generate iPS will also need to be addressed.

In recognition of the rapid development of the field of gene therapy, the CHMP Working Parties, the European Directorate for Quality of Medicines and the International Conferences of Harmonization have constantly developed and updated a number of guidelines, reflection papers, and European Pharmacopoeia (Ph. Eur.) chapters (further referred in Section 9), to address specific issues raised in gene therapy medicinal product development and identified from provision of scientific advice.

Furthermore, a number of new legal requirements have recently come into place, including a new legal framework for advanced therapy medicinal products, the legal requirements for shedding studies and environmental assessment and the introduction of risk-based approach of advanced therapy medicinal products. Therefore, in addition to reflect scientific development in the field of gene therapy, a revised Guideline is also required.

4. RECOMMENDATION

The GTWP recommends a multidisciplinary revision of the current Note for Guidance with the aim:

- to reflect the significant development and experience gained,
- to consolidate, update if required and cross-reference all available guidelines and recommendations that are specific to gene therapy medicinal products, and
- to encompass the requirements related to the introduction of the new legislation (i.e. Regulation (EC) No 1394/2007, amended Directive 2001/83/EC).
- to focus the revision on the common issues related to product classes.
- to cover development genetics, production, purification, characterisation, quality control and comparability in the quality aspects of gene therapy medicinal products
- to provide general considerations as well as specific considerations in quality, non-clinical and clinical aspects of specific classes of gene therapy medicinal products.

5. PROPOSED TIMETABLE

It is anticipated that a draft revised guideline will be available within 12-18 months after adoption of the concept paper and will be released for 6 months external consultation, before finalization within a further 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The revision of the current Note for Guidance will be led by the GTWP in collaboration with Biological Working Party (BWP - responsible for quality aspects) and Safety Working Party (SWP - consulted for non-clinical aspects). Cell-based Product Working Party (CPWP) will be consulted on specific areas of competence. A coordinating team will be appointed with representation from the above working parties. Other relevant working parties e.g. Pharmacovigilance Working Party, Efficacy Working Party, Vaccine Working Party; relevant scientific committees e.g. Committee for Advanced Therapies, Pediatric Committee, CHMP; and external parties will be consulted as needed.

Based on the multidisciplinary nature of this revision, it is considered that a minimum of 2 drafting groups are necessary: 1 focusing on the revision of quality aspects driven by the BWP, 1 focusing on non-clinical and clinical aspects, driven by GTWP.
Drafting work will be conducted primarily by email and teleconferences; although it is considered that 1 face-to-face drafting group meeting may be needed for Quality. The GTWP, BWP, CPWP and SWP will discuss draft versions at their regular meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

The revised Guideline will harmonise data requirements for applicants and ease assessment for regulators. It may contribute to streamline the development and ultimately marketing authorisation of applications of gene therapy medicinal products via the centralised procedure.

8. INTERESTED PARTIES

Pharmaceutical industry and academic or other developers of gene therapy medicinal products, academic networks and learned societies involved in the area.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Guideline on development and manufacture of lentiviral vectors (CHMP/BWP/2458/03)

- Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006)
- Draft guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Concept paper on the development of a guideline on the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified cells (EMEA/CHMP/GTWP/405681/2006)
- Draft reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (EMEA/CHMP/GTWP/587488/2007)
- Draft ICH Considerations on Oncolytic viruses (EMEA/CHMP/GTWP/607698/2008)
- Draft guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (EMEA/CHMP/VWP/141697/2009)
- European Pharmacopoeia - General chapter 5.14. on Gene transfer medicinal products for human use
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products
- Draft Commission Directive *(published by the European Commission on 2nd April 2009)* amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.
- ICH Considerations on the General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors