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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE QUALITY, PRECLINICAL AND CLINICAL ASPECTS OF MEDICINAL PRODUCTS CONTAINING GENETICALLY MODIFIED CELLS

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INTRODUCTION

Medicinal products for advanced therapies include products for gene therapy as well as for cell therapy developed in recent years with the aim of treatment or prevention of a variety of human diseases.

Medicinal products for advanced therapies are defined in Annex I, Part IV, to Directive 2001/83/EC, as amended; gene therapy medicinal products are defined in section 1, while cell therapy medicinal products are defined in section 2.

Guidance on the requirements for marketing authorisation applications of gene therapy medicinal products, including those containing genetically modified cells, is already available in the EU in the Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99). Guidance on cell therapy medicinal products is currently in public consultation (Guideline on human cell-based medicinal products; EMEA/CHMP/410869/2006) based on a previously adopted document (CPMP/BWP/41450/98 Points to consider on manufacture and quality control of human somatic cell therapy medicinal products), and recent developments in this area.

1. PROBLEM STATEMENT

Genetic modification of cells is intended to result in expression of one or more diagnostic, preventive or therapeutic genes, but may also result in expression of additional homologous or non homologous functional properties not previously expressed.

The following are some examples of investigational medicinal products containing genetically modified cells: dendritic cells or other immune cells genetically modified with immune-stimulating genes for tumour immunotherapy; genetically modified autologous haematopoietic progenitor cells for the treatment of monogenic diseases (e.g. SCID) or of cardiovascular diseases; genetically modified autologous chondrocytes administered for cartilage repair; genetically modified osteogenic cells to repair bone fractures; progenitor or mature haematopoietic cells genetically modified with genes inhibiting entry or replication of pathogens, administered for the treatment of infectious diseases; marker gene expressing haematopoietic cells used for in vivo marking studies, for in vivo diagnosis and to monitor differentiation of cells.

The quality, safety and efficacy of medicinal products containing genetically modified cells are linked to this dual nature: the phenotype of the cell and its alteration by genetic engineering.

Production, characterisation, non-clinical studies and clinical monitoring of medicinal products containing genetically modified cells should be designed and conducted taking into consideration the cell population structure and function as well as the genetic modification. A strictly controlled process from preparation of vector to genetic modification of cells and up to product use at clinical level is imperative, in order to avoid risks for the recipient (such as for example in vivo selection of an aberrant clone following insertional oncogenesis or vector dissemination from target cells) and to properly address environmental risk, whose assessment is a specific requirement for these medicinal products.

Consequently, clear and comprehensive requirements are needed in order to ensure that when the medicinal products containing genetically modified cells reach the patients they are of the highest possible quality.

2. DISCUSSION (ON THE PROBLEM STATEMENT)

The guideline on cell-based medicinal products, which is being developed by CPWP, is intended to cover general aspects of human cell based medicinal products. However, the clinical use of genetically modified cells raises specific issues which include, but are not limited to, the type of vector used for genetic modification, transduction and transgene expression efficiency in relation to clinical efficacy, expected/unexpected phenotype modification, genetic stability, insertional oncogenesis, vector shedding/mobilisation, the *in vivo* fate of the cells/transgene product, bystander effects, cell survival time, cell homing and the use of gene-modified cells for molecular imaging.

The Note for Guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) describes requirements applicable to all types of gene transfer medicinal products. It was issued when the field was relatively underdeveloped and now requires updating in light of recent scientific advancements and of experience gained in this area. Other guidance documents that have been subsequently developed (such as those covering lentiviral vector development, non clinical studies, germ line transmission risk and environmental risk assessment) cover only some of the issues raised by the clinical use of genetically modified cells.

Additional and specific guidance is required to assist both the manufacturers (during development, production and quality control of medicinal products containing genetically modified cells) and for regulators in charge of control and assessment activities. Such updated and focussed guidance is lacking on aspects pertaining to quality, manufacturing, non-clinical and clinical issues, as well as the environmental risk assessment, that are specific for this type of medicinal products.

Ideally this should be presented as a stand-alone document that will describe all the specific requirements for medicinal products containing cells that have been genetically modified.

The guideline would also be applicable to cell medicinal products where the cells have been genetically modified for purposes other than for a medicinal effect, for example, for enhanced manufacturing properties.

3. RECOMMENDATION

The Gene Therapy Working Party recommends the development of a specific European guideline on the requirements for medicinal products containing genetically modified cells, thus achieving both the needed revision of the Note for Guidance CPMP/BWP/3088/99 for quality issues of medicinal products that contain genetically modified cells and the necessary complementation of the guideline on human cell based medicinal products under development. The proposed guideline will focus on issues specific to genetically modified cells in order to avoid duplication of and discrepancies with the Guideline on human cell-based products.

A guideline is a sufficiently flexible document to accommodate the fast-paced scientific progress of this field.

The guideline will cover quality, non-clinical and clinical aspects, providing guidance for example on the following issues: development genetics of the transducing vector, characterisation of the inserted gene and of the expressed product, gene copy number per cell, use of molecular design to increase vector safety, expected/unexpected phenotype modification, genetic stability, insertional oncogenesis, the *in vivo* fate of the cells/transgene product, transduction efficiency, bystander effects, cell survival time, persistence and regulation of transgene expression, biodistribution, use of genetically modified cells for molecular imaging, use of molecular methods in clinical monitoring, vector shedding, vector mobilisation and short-term clinical follow-up.

4. PROPOSED TIMETABLE

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

5. RESOURCE REQUIREMENTS FOR PREPARATION

The guideline development will be led by GTWP in collaboration with CPWP. A joint drafting group will be appointed with members from GTWP and CPWP, SWP and BWP.

Other relevant working parties, e.g., EWP, and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. GTWP, CPWP, BWP and SWP will discuss draft versions at their regular meetings. It is anticipated that at least two sessions at plenary GTWP-meetings in 2007 will be needed before the draft is finalised.

6. IMPACT ASSESSMENT (ANTICIPATED)

The guideline will give applicants and Regulatory Authorities guidance on the assessment of medicinal products containing genetically modified cells. Such a harmonized approach will contribute to protect European patients and to foster the development of cell-based gene therapy medicinal products use in EU. It will also streamline their clinical development and ultimately marketing authorisation applications via the centralised procedure.

7. INTERESTED PARTIES

EMEA: GTWP, CPWP, BWP, SWP.

External consultation: pharmaceutical industry, academic networks and learned societies within the EU.

8. REFERENCES TO LITERATURE, GUIDELINES ETC

Regulation 726/2004
Directive 2001/20/EC
Directive 2003/63/EC amending, Annex I, part IV to Directive 2001/83/EC
Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)
Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)