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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE RISK-BASED APPROACH ACCORDING TO ANNEX I, PART IV OF DIR. 2001/83/EC APPLIED TO ADVANCED THERAPY MEDICINAL PRODUCTS

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1. INTRODUCTION

The aim of the risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC is to determine the extent of data required for Marketing Authorisation Application (MAA) for an advanced therapy medicinal product (ATMP). The risk-based approach is based on the identification of risk factors inherent to the nature of the ATMP in question and associated with its quality, safety and efficacy. The risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC should be distinguished from Risk Management, and the benefit / risk assessment in the context of a marketing authorization evaluation. The risk-based approach, when applied to the development program should be described and justified in Module 2 of the Marketing Authorisation Application dossier.

The risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells, the manufacturing process, and the biological characteristics of used vectors, the properties of protein expression, non-cellular components and the specific therapeutic use of the ATMP. Thus the manufacturing process including in-process testing and batch release testing should be adequate to limit the risk of the ATMP. Nonclinical and clinical testing should further address the identified risk factors.

2. PROBLEM STATEMENT

The guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and the Note for Guidance on gene transfer medicinal products (CPMP/BWP/3088/99) addressed the manufacturing and quality control as well as non-clinical and clinical development of respectively cell-based medicinal products (which includes somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products. Revision of Annex I part IV of Directive 2001/83/EC, which followed the entry into force of Regulation (EC) No. 1394/2007 for ATMPs, introduced the concept of the risk-based approach. However, no detailed guidance on the practical application of the risk-based approach and the consequences for the product development are available so far. Moreover, there is a necessity to familiarise the stakeholders, future applicants, National Competent Authorities as well as consumer with this concept.

This concept paper is intended to provide the background and rationale of the guideline on the risk-based approach and shall describe the approach and content of the future guideline.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The use of ATMPs may be associated with certain risks, which are linked to several risk factor related to the Quality, biological activity and administration of the ATMP. Individual risk factors shall be discussed in order to enable a conclusion on the overall risk of the ATMP.

A non-exhaustive list of risk factors for cell-based and gene therapy medicinal products is given below:

Cell based medicinal products:

Risk factors, e.g.

- The cells used including cell source, cell type and differentiation status
- All aspects of the manufacturing process including manipulation
- The non-cellular components
- The specific therapeutic use including mode of administration, duration of exposure

The risk factors may be linked with risks such as

- Unwanted immune responses as target or effector cell
- Genetic instability and tumorigenicity of the cells used
- The transmission of viruses and adventitious agents
- Undesired immunogenic, pyrogenic or toxicological reactions by non-cellular components
- Unintended biological responses of the product

Gene therapy medicinal products:

Risk factors, e.g.

- Potential for and extent of chromosomal integration of a vector
- Capacity of a vector/ gene for latency/ reactivation
- Capacity of a vector for inadvertent replication after complementation by viruses causing escape from latency and reactivation and eventually leading to mobilisation
- Replication incompetence or competence of a vector
- Potential for recombination or re-assortment
- Altered expression of (a) host gene(s)
- Transgene expressed and its duration
- Biodistribution
- Potential for shedding and transmission

The risk factors may be linked with risks such as

- Unwanted immune responses
- Tumorigenicity
- Infection
- Unintended biological responses of the product

4. RECOMMENDATION

The CPWP and GTWP recommend drafting a guideline on the application of the risk-based approach for ATMPs. It is proposed that the guideline has two separate sections on aspects specific to cell-based medicinal products and gene therapy medicinal products, respectively. Furthermore aspects regarding combined ATMPs will be addressed.

The guideline is intended to provide an approach on how to identify and describe the risks of an ATMP in the MAA dossier. It is not the intention to provide a rigid classification system of different risks but rather to exemplify the concept by using several examples with different risk profiles (i.e. a genetically modified stem cell product of allogeneic and/or xenogeneic nature or an autologous cell-based product of locally administered differentiated cells).

It is foreseen that the application of the risk-based approach shall follow the following basic steps:

1) **Risk Identification of the ATMP:**

   The Applicant is asked to propose a systematic process for the identification and discussion of risks to the quality, safety and efficacy of an ATMP. The risk shall be based on individual risk factors, such as the ones listed above. The Applicant's conclusion on the degree of risk should be thoroughly justified on the basis of scientific data underpinning identified risk factors.

2) **Consequences for the extent of data in the MAA dossier:**

Based on the identification and discussion of the risk of an ATMP, the Applicant should justify the extent of quality, non-clinical and clinical data presented for Marketing Authorisation Application and provide an overview of the implement in the MAA dossier. The extent of data shall take into account the technical requirements for ATMPs as described in Annex I, part IV of Dir. 2001/83/EC. Depending on the risk of the product certain chapters may be emphasised and complemented with additional data, where necessary, or limited when appropriately justified on the basis of the risk.

In order to address these risks, certain minimisation activities need to be conducted and measures implemented during the product lifecycle.

The approach described in this guideline should enable the applicant to establish an adequate development strategy for an ATMP, including but not limited to adequate in-process controls, setting of specifications, non-clinical data and clinical data requirement. These issues will also be illustrated by examples of products with different risk profiles.

Within the MAA dossier, the risk-based approach shall be placed into Module 2 of the Common Technical Document as a supplement to the quality, nonclinical and clinical overall summaries. Further guidance to applicants on the practical aspects of the chapter on the risk-based approach will be provided in the guideline.

5. PROPOSED TIMETABLE

It is anticipated that a draft 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 development of a guideline on the risk based approach will be led by CPWP and GTWP (1 common coordinating drafting group) in collaboration with BWP (consulted for quality aspects), with SWP (consulted for non-clinical aspects), with PhVWP (consulted on the complementarity of this approach with the risk analysis and risk management activities in place), and in compliance with directions given by the CAT. Other relevant working parties and relevant scientific committees e.g. PDCO and CHMP and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The relevant working parties will discuss draft versions at or in the margin of their regular meetings.
Based on the multidisciplinary nature of this revision, it is considered that a minimum of two dedicated face-to-face drafting group meeting will be necessary.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline on the application of the risk-based approach is expected to clarify the process (analysis, methodology, and presentation) of the determination of the extent of data requirements needed for marketing authorisation application of an ATMP. The guideline is also intended to help regulators in the assessment of the MAA dossier. It may contribute to streamline the development, enabling the applicant to establish an adequate development strategy and ultimately marketing authorisation of applications of ATMP via the centralised procedure.

8. INTERESTED PARTIES

Pharmaceutical industry and academic or other developers of ATMPs, academic networks and learned societies involved in the area.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products
- Commission Directive Commission Directive 2009/120/EC of 14 September 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.
- Guideline on Human Cell-based Medicinal Products (EMEA/CHMP/410869/2006)
- Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99)
- Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/149995/2008)