QUESTIONS AND ANSWERS RELATED TO THE ASSESSMENT OF SIMILARITY FOR ADVANCED THERAPY MEDICINAL PRODUCTS ("ATMPS") IN THE CONTEXT OF THE ORPHAN LEGISLATION.

FREQUENTLY ASKED QUESTIONS

VERSION 1

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Introduction

Regulation (EC) No 141/2000 on orphan medicinal products[1] was adopted to promote the research, development and marketing of medicinal products for rare diseases. The cornerstone of the Regulation is the principle of market exclusivity. When a marketing authorisation for an orphan medicinal products is granted, the Union and the Member States shall not for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product.

In accordance with Commission Regulation (EC) No 847/2000[2], "similar medicinal product" means a medicinal product containing a similar active substance(s) as contained in an authorised orphan medicinal product and which is intended for the same therapeutic indication. In light of developments in the field of biological medicines, in particular in the field of advanced therapy medicinal products, the definition of "similar active substance" has been revised.[3]

This Q&A document provides practical guidance to developers of ATMPs on the application of the concept of "similar active substance". Throughout this document the term "similarity" is used to refer to the assessment whether two active substances are similar within the meaning of Commission Regulation (EC) No 847/2000. It is stressed that the content of this document cannot be extrapolated to products other than ATMPs, or to draw conclusions regarding comparability between two ATMPs in a context other than the application of the orphan legislation.

The responses provided in this document are not intended to replace the Commission Regulation (EC) No 847/2000 or to provide "interpretation" beyond its intent. The content of this document is without prejudice to a different interpretation that may be issued by the European Court of Justice.

The document will be updated to reflect new developments.

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p.1).
[2] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ L 103, 28.4.2000, p.5).
[3] Commission Regulation (EU) 2018/781 of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product' (OJ L 132, 30.5.2018, p. 1)

1. Does the route of administration play a role in the assessment of similarity?

The route of administration cannot be considered in the assessment whether the active substances of two medicinal products are similar or not. This principle also applies to ATMPs.

There may be cases where a different route of administration can bring a therapeutic advantage for patients. In such a case, in order to obtain a marketing authorisation when a similar medicinal product has already been granted an orphan marketing authorisation, the applicant should demonstrate that the medicinal product which is administered *via* a different route of administration is clinically superior as provided for under Article 8(3)(c) of Regulation (EC) No 141/2000.

It is recalled that the definition of clinical superiority is provided for under Article 3(3)(d) of Commission Regulation (EC) No 847/2000.

2. In the case of ATMPs, differences in the manufacturing technology can be relevant to demonstrate non-similarity between two products. What is the meaning of "manufacturing technology"?

Certain technological changes to the manufacturing process of ATMPs can justify a finding of non-similarity. The following examples (non-exhaustive list) illustrate differences in manufacturing technologies that could support a claim of non-similarity, provided that those changes lead to a significant impact on the biological characteristics and/or biological activity which is relevant for the intended therapeutic effect and/or safety attributes of the product:

- CD34+ cells transduced with a viral vector could be considered to be non-similar to CD34+ cells transduced with gene editing technology, even if both products target the same indication.

- Having regard to the different precision, efficiency, and specificity profiles of the different meganuclease-based engineering technologies, a gene therapy medicinal product developed with zinc-finger nucleases and a gene therapy medicinal product developed with CRISPR-Cas9 could be considered to be non-similar, even if they target the same DNA sequence.

- Dendritic cells activated with a tumour lysate could be considered to be non-similar to dendritic cells activated by means of purified tumour protein, even if both products target the same indication.

It is stressed that not all changes to the manufacturing process can qualify as a change in manufacturing technology. For example, a change in manufacturing process (*e.g.* cultivation of cells in an open system *vs.* a closed system; change in the number of cell passages) or a change in equipment (*e.g.* upgraded bioreactor) generally cannot support a finding of non-similarity.

3. Which safety attributes are relevant for the purposes of assessing similarity between two ATMPs?

Only safety attributes that provide a meaningful advantage for the patient can be considered to support a claim of non-similarity. For example, the addition of a suicide gene in a gene therapy medicinal product can only be taken into account if this feature is relevant to the patient having regard to the targeted disease and specific product characteristics. Thus, the inclusion of a suicide gene in a product that consists of cells with a short survival period *in vivo* would not be considered relevant to support a claim of non-similarity.

It is generally expected that claims of distinct safety attributes are supported by data to determine that these are likely to be of clinical relevance. Such data may be *in vitro* / *in vivo* non-clinical data or clinical data. Exceptionally, robust published scientific evidence may be considered.

4. Are all differences in the therapeutic sequence, viral vector, transfer system, or regulatory sequences relevant for the purposes of assessing similarity between two gene therapy medicinal products?

Only differences that have an impact on the therapeutic effect and/or the safety attributes can support a claim of non-similarity. For example, the addition of silent base pair changes and codon optimisation not leading to a change of amino acid sequence or having other functional effect would not be considered relevant to support a claim of non-similarity.