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 2

Document history	Date	Description of main changes
Version 1	25 May 2018	
Version 2	13 April 2021	Addition of new questions and examples based on accumulated experience.

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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 product 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 ("ATMPs"), 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 guidance beyond the scope above-referred. The content of this document is without prejudice to a different interpretation that may be issued by the Court of Justice of the European Union.

The document will be updated to reflect new scientific 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 safer, more effective or otherwise 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 conclusion of non-similarity. The following examples (non-exhaustive list) illustrate differences in manufacturing technologies that could support a claim of non-similarity, where it can be anticipated that there is a significant impact on the biological characteristics and/or biological activity 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 substitute or modify the same genetic sequence or target the same indication.

- Having regard to the different precision, efficiency, and specificity profiles of the different nuclease-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.

- A cell-based product could be considered to be non-similar if a difference in cell isolation or selection procedure results in improved consistency of the composition of the active cell population that is relevant for the benefit/risk profile of the product.

- A product may be considered to be non-similar if a difference in the manufacturing process permits expanding the treatable population (within the

same targeted therapeutic indication), such as *e.g.* the possibility to treat patients with lower initial starting material target cell counts.

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 conclusion of non-similarity, unless it is demonstrated that the change leads to a significant impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.

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.

However, the introduction of an ablation mechanism may support a claim of non-similarity in cases where the ablation of the therapy may be useful to address toxicities derived therefrom. In addition, differences that reduce the risk of immune responses, insertional mutagenesis or formation of replication competent viruses, as well as differences associated with the vector integration profile may also support a claim of non-similarity.

4. Are all differences in the therapeutic gene 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 a significant impact on the intended therapeutic effect and/or the safety attributes of the product can support a claim of non-similarity. For example, the addition of silent base pair changes not having a functional effect would not be considered relevant to support a claim of non-similarity.

The following examples (non-exhaustive list) illustrate differences that could support a claim of non-similarity, where it can be anticipated that there is a significant impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product:

For viral vectors for *in vivo* gene transfer:

- Differences at the level of the virus capsid that reduce immune responses, improve cellular uptake or impact tissue tropism.

- Differences at the level of the virus capsid that permits expanding the treatable population (within the targeted therapeutic indication), for example due to lower sensitivity to pre-existing anti-capsid neutralizing antibodies.

- Differences at the level of the viral sequence that reduce the risk of insertional mutagenesis or the risk of formation of replication competent viruses, as well as differences associated with the integration profile.

- Differences at the level of the therapeutic gene or regulatory sequences (*e.g.* promoter) that increase the level of expression of the therapeutic protein, stability, tissue tropism or transduction efficiency.

- Differences at the level of the therapeutic gene sequence that have an impact on function or stability of the encoded protein.

For ex-vivo gene therapy products:

- Differences at the level of the virus capsid or viral sequence that impact the transduction profile or composition of the transduced cell population, as well as differences that increase transduction efficiency.

- Differences at the level of the viral sequence that reduce the risk of insertional mutagenesis or the risk of formation of replication competent viruses, as well as differences associated with the integration profile.

- Differences at the level of the therapeutic gene or regulatory sequences (*e.g.* promoter) that increase the level of expression of the therapeutic protein or stability.

- Differences at the level of the therapeutic gene sequence that have an impact on function or stability of the encoded protein.

5. What differences in the starting materials may be considered relevant to support a claim of non-similarity?

As indicated in Question 4, differences in the vector that is used as starting material for the manufacture of ex-*vivo* gene therapy products may be considered relevant to support a claim of non-similarity.

The following examples (non-exhaustive list) illustrate other differences in starting materials that could support a claim of non-similarity, where it can be anticipated that there is a significant impact on the biological characteristics and/or biological activity that is relevant for the intended therapeutic effect and/or safety attributes of the product:

- The use of primary cells *vs* the use of a cell line.

- The use of autologous cells *vs* the use of allogeneic cells.

- Differences in the cell source, for example in the case of cell-based products containing mesenchymal stromal cells derived from different tissues or different sources (adult *vs* foetal).

- The use of a tumour cell line *vs* the use of a non-tumour cell line.

6. Can a difference in principal molecular structural features be considered relevant to support a claim of non-similarity?

Principal molecular structural features can be addressed in the context of the final composition of the product. Specifically, to the extent that principal molecular structural features can be defined for an ATMP, differences at the level of principal molecular structural features can support a non-similarity claim if such differences significantly impact on the biological characteristics and /or biological activity relevant for efficacy and/or safety profile of the product. For example, in the case of CAR T-cells, differences at the level of the CAR construct may support a claim of non-similarity.

7. What level of evidence should be provided to demonstrate that differences in the biological characteristics and/or biological activity are relevant for the intended therapeutic effect and/or safety attributes of the product?

It is acknowledged that information about the manufacturing process and other elements relevant to determine the similarity between two active substances for ATMPs may be confidential and therefore not be available in the public domain. Applicants should address the assessment of similarity with a previously authorised ATMP on the basis of the information that is publicly available or that is otherwise accessible to the applicant.

The claim that differences in the biological characteristics and/or biological activity are significant and relevant for the intended therapeutic effect and/or safety attributes of the product should be based on plausible scientific grounds *e.g.* on the basis of scientific literature or available in-vitro data/ in-vivo (non-)clinical data. Clinical data may be used -if available- but the generation of clinical data is not required. It is stressed that the assessment of similarity between two active substances does not entail demonstration that the new product is safer, more effective or otherwise clinically superior to a previously authorised product as provided for under Article 8(3)(c) of Regulation (EC) No 141/2000.

Additionally, it is noted that differences on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the products may be considered "significant" even if they are only relevant for a subset of the intended population.

Applicants are not required to demonstrate non-similarity against all of the parameters referred in Section (3) of Article 3(3) of Regulation (EC) No 847/2000. A finding of non-similarity will be upheld if a single difference has been identified that has a significant impact on the biological characteristics and/or biological activity of the product relevant for the intended therapeutic effect and/or safety attributes thereof. It is stressed that, in addition to the similarity assessment in accordance with Section (3) of Article 3(3) of Regulation (EC) No 847/2000, applicants should provide an assessment whether their product has the same therapeutic indication as a previously authorised orphan medicinal product.