



Submission of comments on the Consultation Document

CONCEPT OF 'SIMILAR MEDICINAL PRODUCT' IN THE CONTEXT OF THE ORPHAN LEGISLATION: ADAPTATION TO TECHNICAL PROGRESS

Comments from

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EUCOPE RESPONSE TO THE CONSULTATION DOCUMENT TO THE REVIEW OF THE CONCEPT OF ‘SIMILAR MEDICINAL PRODUCTS’ IN THE CONTEXT OF THE ORPHAN LEGISLATION

Introduction

The European regulatory framework, the incentives as defined in the Orphan Medicinal Product Regulation (EC) 141/2000¹ and the accompanying Commission Regulation EC 847/2000² have successfully stimulated research and development of orphan medicinal products. Until 2000, research for therapies treating rare diseases was scarce due to the complexities of research and the limited commercial attractiveness linked to the small number of patients per disease. As a positive result of the Regulation, 122 orphan medicinal products have been authorised (including 118 orphan designations),³ providing patients with treatments for a variety of severe and life threatening rare diseases. Before the adoption of Regulation (EC) 141/2000 only eight orphan-like medicinal products were approved. As of today, there remains a lot of work to be done to develop new treatments for patients with rare diseases; thousands of diseases still have no approved treatment and new diseases are being classified as the science evolves. As the Commission recently stated: “*The number of products authorised has grown over the years (which is encouraging for the future), but remains limited bearing in mind the existence of 5,000 to 8,000 distinct rare diseases [...]. The incentives of the orphan drug legislation are therefore essential to facilitate pharmaceutical development.*”⁴ To preserve this objective, it is crucial to maintain a favourable and predictable environment that effectively stimulates research in this field.

Consultation document text:	EUCOPE comments and proposed amendments
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¹ [REGULATION \(EC\) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products](#)

² http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf

³ http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2016/10/WC500214188.pdf

⁴ http://ec.europa.eu/health/files/orphanmp/doc/orphan_inv_cwd_20160126.pdf (page 4)

Consultation item: Removal of the definition of active substance	<u>Comment</u> EUCOPE understands the Commission’s intention to remove the definition of ‘active substance’ as Article 8(4) of Regulation (EC) No. 141/2000 does not empower the Commission to define such term. It is therefore understood that such removal aims at complying with the mandate provided to the EC by the existing legislation.
Consultation item: Definition of similar active substance	
1. Chemical medicinal products	<i>No comments</i>
2. Biological medicinal products	<u>General comments:</u> Biologics’ manufacturing processes can be different but resulting in similar products. This element should be more appropriately addressed in the text under revision. We recommend amending the text in a way that clearly confirms the ‘similarity’ in case of manufacturing change for a synthesized biological product. Additionally, EUCOPE would like to stress that it is necessary to focus on both the structural and the functional activity differences when determining similarity. Biological products cannot be considered as identical in their structure, given the sensitivity of these therapies to external elements in the development process (e.g. environment conditions). Assessing the similarity of these products on the basis of structural details only would not fully grasp the specificities of these products and would not guarantee functional equivalence. <u>Amendment proposals:</u> 54-58: The principal molecular structural features are the key structural components of an active substance that impart one or more desired biological activities. The features may be whole or part of the

functionality of that substance. The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element or structural elements significantly contributing to the functionality of the active substance.

64-81: Biological active substances that differ from the original biological substance only with respect to minor changes in the molecular structure such as:

- proteinaceous substances:

- If the difference is due to infidelity of transcription or translation should normally be considered similar.

- If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) should be normally considered similar. However, the addition of an extensive glycan structure to the active moiety for example improving the binding capacity of the substance may result in a non-similar substance.

- If the difference in the amino acid sequence is not major should normally be considered similar. Therefore, two pharmacologically related protein substances of the same group for example having differences related to e.g. n-terminal methionine, naturally extracted versus rDNA derived proteins (or other minor variants)

molecule. The active substance may possess a set of key principal molecular structural features that import one desired biological activity and another set of key principal molecular structural features that impart another desired biological activity. are relevant for the functionality of that substance.—The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element or structural elements significantly contributing to the functionality of the active substance.

Justification:

Changes in the structural features of the “similar active substance” need to be linked to a functional effect/biological activity to determine whether molecules are similar.

64-81: “Biological active substances that differ from the original biological substance only with respect to minor changes in the molecular structure such as:

- proteinaceous substances:

- If the difference is due to infidelity of transcription or translation should normally be considered similar.

- If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) should ~~be~~—normally **be** considered similar. However, **some post-translational modifications may result in a non-similar substance for example** the addition of an extensive glycan structure to the active moiety **for example leading to an improving improvement in** the binding capacity of the substance ~~may result in a non-similar substance.~~

- If the difference in the amino acid sequence is not major should normally be considered similar. Therefore, two pharmacologically related protein substances of the same group for example having differences related to e.g. n-terminal methionine, naturally extracted versus rDNA derived proteins (or other minor variants) would

would normally be considered similar. However, the addition of a structural element which is for example a conjugated amino acid sequence in rDNA derived proteins may be considered non-similar.

82-86: - Monoclonal antibodies binding to the same target epitope would normally be considered similar. However, two monoclonal antibody conjugates or fusion proteins would be determined to be non-similar if either the CDR-sequences of the antibody or the additional structural element of the conjugated monoclonal antibody were different.

normally be considered similar. However, the addition of a structural element which is for example a conjugated amino acid sequence in rDNA derived proteins may be considered non-similar **if it significantly affects the biological and functional characteristics of the product.**

Justification:

The paragraph, in particular line 81, requires more precise language. It should be clear that the addition of a structural element in rDNA derived proteins that does not have any impact on the biological characteristics or functionality of the product should not be decisive on non-similarity. In accordance with lines 54-55 of the Consultation Document, only additional structural elements or structural elements significantly contributing to the functionality of the active substance are recognized for the definition of “the principle molecular structural features”, which is considered one of the two decisive criteria in similarity assessment.

As regards post-translational events, the paragraph discriminates between different modern technologies often used for the same purpose, i.e. between a pegylated molecule – which would be deemed similar to the original – and an Fc-molecule, deemed different, even if, in both cases the outcome of the modification is a longer-acting compound.

82-86: ~~Monoclonal antibodies binding to the same target epitope would normally be considered similar. However,~~ Two monoclonal antibody conjugates or fusion proteins would be determined to be non-similar if either the CDR-sequences of the antibody **are different or the additional structural element of the conjugated **or fused** monoclonal antibody **or other functionally relevant sequences (e.g. the Fc part of antibodies recruiting CDC or ADCC) are different, provided that the modification to the additional structural element or other functionally relevant sequences significantly affects the biological and functional characteristics of the product.****

Justification:

We welcome an update of the definition for monoclonal antibodies. In particular, we welcome and agree that the CDR sequences and

<p>87-94: - polysaccharide substances:</p> <ul style="list-style-type: none"> - If the substances have identical saccharide repeating units, even if the number of units varies should normally be considered similar. - A conjugated polysaccharide vaccine compared to a non-conjugated polysaccharide vaccine containing the same antigen is considered a non-similar substance. Two conjugated vaccines derived from the same antigen and using similar methods of modification or conjugation technology would be considered similar substances. 	<p><i>additional structural elements are decisive for the functionality of the monoclonal antibody and should be considered the key elements to distinguish between different monoclonal antibodies. The CDR sequences and additional structural elements are very precise characteristics of monoclonal antibodies that can be, and typically are, described early in monoclonal antibody development. For better precision, lines 83-86 require small modifications.</i></p> <p><i>The first sentence of the definition (lines 82-83) should be deleted. An assessment of similarity based on binding to the same epitope is problematic as the precise binding target for two monoclonal antibodies might not be known at the time of similarity assessment. It may be difficult and a long-term effort to thoroughly characterize target epitopes for monoclonal antibody. This is contrast to the CDR sequences that are characterized early in monoclonal antibody development. We also note that the first sentence of the definition has been carried over from the current wording of Regulation 847/2000 probably without being thoroughly assessed against the currently proposed part of the definition. In consequence, the first sentence makes the definition highly ambiguous and should therefore be deleted.</i></p> <p>87-94 - polysaccharide substances:</p> <ul style="list-style-type: none"> - If the substances have identical saccharide repeating units, this should normally be considered similar- unless the difference in the number of units significantly affects the biological and functional characteristics of the product. - A conjugated polysaccharide vaccine compared to a non-conjugated polysaccharide vaccine containing the same antigen is considered a non-similar substance. Two conjugated vaccines derived from the same antigen and using similar methods of modification or conjugation technology would be considered similar substances. <p><i>Justification:</i></p> <p><i>The number of units in the polysaccharide substance can possibly impact the biological and functional characteristics of the substance including for example its immunogenicity; therefore, we suggest adding the following language in line 89 to reflect on this possibility: "unless the</i></p>
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	<p><i>difference in the number of units significantly affects the biological and functional characteristics of the product.”</i></p> <p><i>The paragraph on polysaccharide vaccines should be deleted from the list of examples, as it does not take into consideration the complexity of biological molecules such as conjugated antigens.</i></p> <p><i>The physicochemical and biochemical characterization of polysaccharide conjugate vaccines is difficult, and even if derived from the same antigen or using similar methods of conjugation, the resulting immunogenicity properties of two vaccines can differ.</i></p>
<p>3. Radiopharmaceutical medicinal products</p>	<p><u>No comments</u></p>
<p>ATMPs/Gene Therapy Medicinal Products/Genetically modified cells</p>	<p><u>General comments:</u></p> <p>The text of the consultation remains quite vague when it comes to the concept of ‘significant impact’ (lines 105, 109) on the biological characteristics of the products. Thus, we would recommend a clarification of the concept of ‘significant impact’ by adding specific guidelines of what this concept refers to (e.g. having a major impact on functionality and biological activity).</p> <p>Within the field of OMPs a balance is needed to ensure innovation without blocking new entrants of clinical relevance. EUCOPE welcomes the introduction of a specific section on Advanced Therapy Medicinal Products (ATMPs), including gene and cell therapy, which allows for continued flexibility to introduce new medicines within this growing field. However, we caution that these fields of research & development are still rapidly evolving, with no precedents for similarity assessment yet, and therefore further defining and agreeing on the similarity criteria for ATMPs is untimely.</p> <p>For these products, both the starting material and the final product may</p>

<p>100: ATMPs for which principal molecular structural features cannot be fully defined and [...]</p> <p>105-106: which have significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product.</p> <p>109-111: - there are differences in the manufacturing technology having a significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product.</p>	<p>be patient-specific and characterization of the product often requires highly specific and proprietary methods, so that similarity resides more in the process and in the controls than in the analytical characterization of the active substance. On this basis, EUCOPE agrees with the use of broad points in the text, and encourages relying instead on the Applicant to scientifically analyse the similarities and differences for the clinical importance of their likely biological effects (both therapeutic and in adverse events profiles).</p> <p><u>Amendment proposals:</u></p> <p>100: ATMPs for which the principal cellular composition or the principal molecular structural features are different or cannot be fully defined and [...]</p> <p><i>Justification:</i></p> <p><i>Line 100 only mentions the principal molecular structure. This is not sufficient, as the difference in principal cellular compositions should also be considered in regard to the assessment of non-similarity.</i></p> <p>105-106: which the Applicant justifies as having significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product.</p> <p>109-111: there are differences in the manufacturing technology the Applicant justifies as having a significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product, or resulting in improved formulation for patient relevant effects, availability and treatment scheme.</p> <p><i>Justification:</i></p> <p><i>Line 109 and following state the significant impact of the manufacturing technology on the biological characteristics. What needs to be taken into account additionally is the possibility of the manufacturing technology not having a significant impact etc. and instead having an improved formulation for patient relevant effects, availability or treatment scheme.</i></p>
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<p>99-116: An active substance is not considered similar in cases of: [...] (bb) two gene therapy medicinal products when there are differences in the therapeutic sequence, viral vector, transfer system or regulatory sequences that significantly affect the biological characteristics and/or activity relevant for the intended therapeutic effect of the product. Minor differences in the therapeutic sequence without a significant impact on the intended therapeutic effect are not sufficient to support the claim that two gene therapy medicinal products are non-similar.</p>	<p>99-116: An active substance is not considered similar in cases of: [...] (bb) two gene therapy medicinal products when there are differences in the therapeutic sequence, which results in molecular structural different elements (e.g. different binding-, linker-, transmembrane-, signaling, regulating structures), viral vector, transfer system or regulatory sequences, or approaches for administration (including administration route) that significantly affect the biological characteristics and/or activity relevant for the intended therapeutic effect of the product. Minor differences in the therapeutic sequence without a significant impact on the intended effect (not resulting in molecular structural different elements) are normally not sufficient to support the claim that two gene therapy medicinal products are non-similar.</p> <p><i>Justification:</i></p> <p><i>Line 113: the line lists requirements for the non-similarity of two gene-therapy products. It does not however recognize molecular structural different elements as a means of determining non-similarity between two gene therapy medicinal products, when there are differences in therapeutic sequence. It also does not recognize the potential impact of changes introduced to improve administration / route.</i></p> <p><i>Line 116: the consultation document refers to minor differences in the therapeutic sequence without a significant impact on the intended therapeutic effect as an indication towards similarity. However, it fails to take into account the possibility of a minor difference in the therapeutic sequence not resulting in molecular structural different elements.</i></p>
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