



EUROPEAN COMMISSION CONSULTATION DOCUMENT

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

Comments from the BioIndustry Association

The BioIndustry Association (BIA) welcomes the opportunity to submit these comments and observations on the European Commission consultation document on the concept of similarity in the context of Regulation (EC) N° 141/2000 on orphan medicinal products.

The BIA is the trade association for innovative enterprises involved in UK bioscience. Members include emerging and established bioscience companies; pharmaceutical companies; academic, research and philanthropic organisations; and service providers to the life science sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and the media. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

The BIA has had sight of the response by the EFPIA-EuropaBio Joint Task Force on Orphan Medicinal Products and Rare Diseases, and supports their submission. Please note the comments below are identical to those provided in the EFPIA-EuropaBio response.

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General Comments:

The Joint Task Force welcomes this consultation document as a necessary step towards clarifying certain provisions of Regulation 141/2000 (hereafter referred to as the Orphan Regulation). The Orphan Regulation and the accompanying Commission Regulation EC 847/2000 have successfully stimulated research and development of orphan medicinal products (OMPs). The Joint Task Force would like to emphasize the vital importance of maintaining a favourable regulatory environment to continue to see progress in treating rare diseases.

It is acknowledged that different criteria are necessary for large and small molecules, and that there have been many technological developments, especially in the area of biological medicines, since the regulation was developed.

Within the scope of the current consultation, the Joint Task Force considers that for the three categories of products highlighted in this consultation: chemical medicinal products, biological medicinal products and radiopharmaceutical medicinal products, the degree of technological change in each area is progressing at differing rates, and thus we agree that a difference in the requirements for demonstrating similarity will differ from product type to product type. In light of this we consider that the changes proposed for chemical medicinal products and radiopharmaceutical medicinal products are appropriate, however the changes proposed for biological medicinal products require further consideration and revision.

Advanced Therapy Medicinal Products

Within the field of OMPs a balance is needed to ensure innovation without blocking new entrants of clinical relevance. The Joint Task Force 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.

For these products, both the starting material and the final product may 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, the Joint Task Force 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).

Monoclonal Antibodies

The Joint Task Force welcomes an update to the definition for monoclonal antibodies, however this paragraph (lines 82 – 86) would benefit from greater clarity, as the complexities of this diverse group of molecules is not properly addressed. In particular, a clear differentiation must be made for two (or more) different monoclonal antibodies designed to act on a common target. Additionally, this paragraph describes fusion proteins and two antibody conjugates as being non-similar, however antibody conjugates molecules which likely combine existing protein molecule and chemical moiety, must also be taken into consideration. We also think that the “two monoclonal antibody conjugates” nomenclature does not effectively describe the diversity of molecules being developed, which may have multi-specific target epitope.

We welcome and agree that the complimentary-determining region (CDR) sequences and 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. However, it should be noted that changes outside the CDR region (e.g. fragment crystallisable region) should also be considered relevant for the assessment of similarity if the changes have an impact.

A “similar active substance”

Changes in the structural features of the “similar active substance” must be linked to changes in a functional effect/biological activity to really determine whether a molecule is similar to the approved product. Additionally, the potential similarity for medicines with more than one active substance (e.g. fixed combinations) should be addressed and clarified in this document. In relation, questions such as how the CHMP will evaluate functional and molecular differences that might have an impact on the safety, efficacy, and/or pharmacokinetic (PK) profile of the medicine, and how will such changes be assessed during a similarity assessment must be considered.

The use of ambiguous terms

The use of ambiguous terms, such as “relevant”, “minor” and “major” must be avoided as they are open to interpretation and do not give adequate guidance to determine the actual boundaries of the definition. For example, when does a “minor” difference become a “major” difference? How can one define whether a structural feature is relevant to functionality? However, when it comes to the use of the word “normally”, found in the recommended change in line 107, the ambiguity is welcomed. The term “normally” in this specific use relates to the onus on the Applicant to convincingly justify that the product presented in the marketing authorisation application is or is not similar to existing therapy, a change the Joint Task Force supports.

Guidance from the CHMP templates

In this new wording it is mentioned that similarity will be conducted by comparison of the chemical structures, but no scientific methodology is proposed as described in the EC guideline and detailed CHMP templates on similarity.

In the above mentioned EC Guideline it is mentioned: “... Software programs may be used to measure the degree of structural similarity between molecules; many of them allowing ‘similarity searching’ to identify molecules having common or similar molecular architectural features (2- or 3-dimensional).”

Additionally, in the CHMP templates it is stated that “...*similarity coefficients using different fingerprints might be used in the evaluation of the similarity of the active substances (chemicals). The values of similarity coefficients using different fingerprints should be discussed. The differences between the similarity coefficients provided by the applicant and the obtained by the rapporteurs should be discussed.*”

The guidance provided in the CHMP templates on similarity is very good and useful for the industry. Therefore, the EC and EMA should clarify even further in this document what type of fingerprints and similarity coefficients should be used by the Applicant. In addition, there are several

other factors, including bitlength for which thresholds should be defined. Moreover, the thresholds considered by CHMP, during the similarity assessment, for the different type of fingerprints should be disclosed in order to avoid surprises during assessment.

LINE-BY-LINE COMMENTS

LINE	COMMENTS
36	<p>Comment: More clarification should be provided on what would constitute minor changes to the active substance, as this wording appears to be very subjective.</p>
54 – 58	<p>Comment: Changes in the structural features of the “similar active substance” need to be linked to a desired or undesired functional effect/biological activity to really determine whether a molecule is similar to the approved product. Additionally, the definition of “Biological Medicinal Product” should also include the structural features as being part or whole of the molecule (as proposed for the “Chemical Medicinal Product”).</p> <p>The “Biological Medicinal Product” may encompass a molecule that has dual functionality, i.e. an Antibody Drug Conjugate (ADC) where the Antibody provides the targeting activity and the warhead provides the toxic activity, or a fusion protein where each component activates a different receptor. Therefore, the structural features definition needs to apply to each moiety separately and as a combination so that both functional/biological activities are covered.</p> <p>Proposed change: The principal molecular structural features are the key structural components of an active substance that are relevant for the functionality of that substance impart one or more desired or undesired biological activities. The features may be whole or part of the molecule. The active substance may possess a set of key principal molecular structural features that impart one desired biological activity and another set of key principal molecular structural features that impart another desired biological activity. 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.</p>
59	<p>Comment: It is suggested to replace the term ‘linked’ with the broader term ‘combined’, as the latter term would cover potential future technologies.</p> <p>Proposed change: Such an additional structural element can be conjugated, fused or linked combined by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids”</p>
69 – 73	<p>Comment:</p>

	<p>It is suggested to delete the sentence “If the difference in structure between them is due to post-translational events” in line 69. This unnecessarily discriminates between different modern technologies often used for the same purpose, i.e. a pegylated molecule would be deemed similar to the original while an Fc-molecule is deemed different even if the goal of the modification was a longer-acting compound.</p> <p>Proposed change: Any post translational modifications resulting in a significant change affecting the biological and functional characteristics of the product, for example 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.</p>
74 – 75	<p>Proposed change: If the difference in the amino acid sequence is not major does not result in a change in functional/biological activity, they should normally be considered similar.</p>
74 – 86	<p>Comment: It is assumed a chimeric, vs. humanized, vs. fully human monoclonal antibody would not be considered similar, even if they bound the same target epitope? This should be further clarified.</p>
81	<p>Comment: This line 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 element 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.</p> <p>Proposed change: ... considered non-similar if it significantly affects the biological and functional characteristics of the product.</p>
82 – 86	<p>Comment: The similarity assessment for a monoclonal antibody should not be based solely on the binding target, as there might be different binding targets for the same monoclonal antibody. In this respect, it is worthwhile to re-consider the wording or inclusion of the first sentence of the definition (lines 82 – 83), as it may prove problematic. Additionally, we strongly believe that the similarity assessment for monoclonal antibodies should in part be based on CDR sequences. Therefore, as the determination of the epitope is dependent on the CDR sequences, this should be reflected in the document.</p> <p>It is not clear why different criteria for non-similarity are used for unmodified monoclonal antibodies versus monoclonal antibody conjugates or fusion proteins. According to the proposals for change contained in the consultation document, two monoclonal antibody conjugates or fusion proteins would be determined to be non-similar if either the CDR sequences or the</p>

	<p>additional structural element were different.</p> <p>Proposed change: Monoclonal antibodies binding to the same target epitope would normally be considered similar. However, Two monoclonal antibodies, 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) were different, if the modification to the CDR sequences, additional structural element or other functionally relevant sequences significantly affects the biological and functional characteristics of the product.</p>
87 – 94	<p>Comment: 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.</p> <p>The vaccine example given in lines 90-94 under the paragraph regarding polysaccharide substances should be deleted: this example is not appropriate as it does not take into consideration the complexity of biological molecules such as conjugated antigens. Biosimilarity between vaccines cannot be defined or characterized in such a simplistic way as it is described in lines 90-94. According to today's state of science it would not be conceivable to consider two vaccines as being biosimilar. Even if two polysaccharide vaccines are derived from the same antigen or are using similar methods of conjugation, the resulting immunogenicity properties of the two vaccines, and thus their intrinsic biological/functional characteristics, are likely to differ.</p> <p>Proposed change:</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 unless there are significant differences in 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.
105 – 107	<p>Comment: In order to conclude whether two related cell-based medicinal products are not similar, it should be clarified whether the applicant needs to <u>justify</u> that the differences in starting materials, or final composition, or manufacturing technology, will result in a significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect, i.e.</p>

	<p>stating the differences alone will not be sufficient.</p> <p>Proposed change: ...which have the Applicant justifies as having significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product. The different source of the starting materials (e.g. as in the case of autologous ATMPs) is not normally sufficient...</p>
109	<p>Proposed change:</p> <ul style="list-style-type: none"> - there are differences in the manufacturing technology the Applicant justifies as having a significant impact
112 – 117	<p>Comment: Consideration should be given to avoid any interpretation of “therapeutic effect” as equating to therapeutic <u>benefit</u>, which could be further considered as “clinical superiority”, required when two orphan drugs are considered similar.</p> <p>Additionally, different approaches for administration of a similar gene therapy medicinal product, in particular using different routes of administration, can translate in very different bioavailability, biodistribution, safety and efficacy profiles. We propose that the text needs to include a mention that differences in the approach for administration to the patients might significantly affect the biological characteristics and functional impact, including the immune response, and/or the activity relevant to the intended therapeutic effect of the product.</p> <p>Proposed change: Two gene therapy medicinal products when there are differences in the therapeutic sequence, viral vector, transfer system, 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 therapeutic effect are not sufficient to support the claim that two gene therapy medicinal products are non-similar.</p>
116	<p>Proposed change: on the intended therapeutic effect or adverse effects are not normally sufficient to support the claim that two gene</p>