Position Paper on the CONCEPT OF 'SIMILAR MEDICINAL PRODUCT' IN THE CONTEXT OF THE ORPHAN LEGISLATION

Date of release: November 2016
FINAL Rev07 (04 NOV 2016)

1. Medicines for Europe general comments

Medicines for Europe, on behalf of the generic, biosimilar and value added medicines industries welcomes the opportunity to comment on the concept of "similar medicinal product" in the context of the Orphan Regulation (EC) No 141/2001.

We fully recognise the importance of available treatments for patients suffering from life-threatening or chronic and seriously debilitating diseases. The experience and benefit delivered to patients over the years, shows the advantage for patients suffering from orphan diseases.

However, as highlighted by the EC in the consultation papers, some issues with the practical application of the legal and regulatory framework associated with the implementation of the Orphan Regulation have been identified. We appreciate the EC's efforts to clarify the interpretation of the Orphan Regulation by reviewing the EC Communication (Articles 3, 5 and 7 of Regulation (EC) N° 141/2000) in February 2016 and followed by the clarification of the concept of similarity in November 2016.

The concept of similarity has a significant impact on the interpretation of Article 8 (particularly Article 8.3 (c) on market exclusivity) in view of the submission of a similar application. Particular issues have been identified with the interpretation of Article 8.1 (acceptance of another application for the same indication in respect of a similar medicinal product only after the expiry of a 10 year market exclusivity) in conjunction with Article 8.3 (c) (derogations) in the context of the follow-on generic/ biosimilar medicinal products after 10 years.

From the generic and biosimilar medicines sectors perspective, the most important is to address the issue of patient access to generic/ biosimilar medicines of those orphan medicines for which 10 years of market exclusivity has already expired, where a new similar orphan medicinal product was approved during the first exclusivity period which then triggered a new exclusivity period, thereby blocking generic launches of the first product for an additional ten years. We trust that this was not the intention of Regulation 141/2000.

Thus, the interpretation of the "similar" medicinal product should not create a mechanism of delaying the authorisation of generic/ biosimilar medicines after the expiry of the legitimate exclusivity for the "initial" orphan

Rue d'Arlon 50 - 1000 Brussels - Belgium
T: +32 (0)2 736 84 11- F: +32 (0)2 736 74 38
www.medicinesforeurope.com

medicinal product's designation. On the other hand, market access of biosimilar medicines should not be blocked by the request for biosimilar medicines to demonstrate that they are not similar to marketed products other than the reference product for orphan indications.

There is also a need to maintain consistency in granting orphan designation and in interpreting "similarity". There are cases where two originator products have the same therapeutic indication, the same mechanism of action and the same principal molecular features. According to the current definition both products are similar. This also has an impact on follow-on generic applications[1].

Although the PIP is not the subject of this consultation, we would like to suggest a clear definition of the deadline by when, at the latest, the paediatric investigation plan (PIP) has to be completed and included in the Product Information (SmPC) of the reference orphan drug product, in order to get the additional two years of market exclusivity as an incentive. It will clearly increase the visibility of reward and predictability on when the generic competition can start.

2. Detailed comments on the concept of "similarity"

Medicines for Europe would like to comment on the proposed European Commission text and to suggest some amendments

Line 1- proposal to remove the definition of the active substance

In principle, we support the removal of the definition of the active substance as suggested by the EC. However, we would like to highlight the necessity to have a specific disclaimer to the definition of the similar active substance in view of the marketing authorisation applications under Article 10.1-4 of the Dir 2001/83/EC. The introduction of such a disclaimer would remove the barrier for the authorisation and market access to generic and biosimilar medicines of those orphan drug designated products, for which 10 years of market exclusivity has already expired. Under the current circumstances, the development of the second generation/ follow-on orphan medicinal product (in accordance with the conditions defined in Article 8.1) has shown to impede the authorisation and patient access to generic/ biosimilar version of the first generation orphan medicinal product[2] beyond the expiry of the 10 year-exclusivity period (especially where the approval of the second orphan product was possible due to the consent of the MA holder (sponsor) only, and no significant benefit had to be shown).

---

[1] Two approved innovator products (Vfend with non-orphan status and Cresemba with orphan drug designation have both the same therapeutic indication (invasive aspergillosis), the same mechanism of action and the same principal molecular features. According to the current definition both products shall be considered similar. In addition to inconsistency, generic medicines applicant cannot refer to the first marketing authorization Vfend which has the same therapeutic indication as Cresemba with an orphan drug status and market exclusivity of 10 years.

[2] One medicinal product was authorised for the treatment of chronic myeloid leukaemia (CML) in adults. The orphan designation CML has already expired. However, generic companies cannot apply for generic MA with CML as indication due to the fact that in the meantime another medicinal product has been authorised by the same MAH for the same orphan designation for CML. Orphan designation for CML granted to the 2nd follow-on orphan product blocks the indication CML for the generic version of the 1st, older product for which the market exclusivity has expired. Linking similarity to "mode of action" (next new tyrosine kinase inhibitors for CML are already in the pipelines) delays generic competition and patient access to a generic version of orphan medicines after expiry of the exclusivity period. This blocks generic version of 1st orphan product for CML much longer (in practice, for 17 years, instead of 10 years). We trust that this was not the purpose of Regulation 141/2000.

Proposed amendment (insertion):
"A medicinal product to be approved in the same therapeutic indication, according to Articles 10.1-4 of Directive 2001/83/EC and referencing a product having no, or having an expired orphan market exclusivity, shall not be considered as a "similar medicinal drug product" in view of Article 8 (1) of the Regulation 141/2000".

Line 13 -Definition of similar active substance

General comments:
Our understanding is that the following criteria for a definition of similarity for an active substance have to be fulfilled (essential requirements for similarity):

1) There has to be a common basic structure of the molecules. Of course, certain modifications (derivatisation in chemistry, unimportant sequence variation in biology) are to be defined as similar, provided that no significant change in 3) or 4) was construed by the modification.
2) The product has to be used in the same indication (disease) and in the same patient group.
3) The similar active substance has to act on the same molecular target.
4) The similar active substance needs to have the same mode of action.

It is for the sponsor to demonstrate, with appropriate evidence that a modified active substance, which would comply with the definitions of similarity 1-4, is nevertheless an improved drug in the sense of "significant benefit". This might be justified on the level of an altered PK/PD, better bioavailability, lower doses, improved safety, etc.
Where sponsors can demonstrate "significant benefit" on the basis of clinical study data, the best case would be that the advantage over existing treatments is statistically significant (superior). However, in many cases of rare diseases, it will be barely achievable for there to be enough patients to reach statistical significance. In such cases, the CHMP has to decide if there is any real benefit.
New pharmaceutical forms alone of already authorised drugs in a given orphan indication should not qualify as having "significant benefit" even if these are somehow advantageous for patients. This would create a tool for strategies to extend the protection provided by the orphan status.

– Chemical medicinal products

Line	**Proposed changes**
34-37	In general Medicines for Europe supports the text in line 34-37 with a suggestion for a minor amendment in red. We recognise that the proposal is in accordance with the current interpretation of the Commission. The proposed definition adds some value but still remains a subject of interpretation and will be open to divergent opinion and subjective viewpoints (as in the case of NAS). As the decision on similarity is linked to incentives, the assessment and rationale for the decision on similarity needs to be fully transparent in the public assessment report. This will increase predictability and certainty in R&D investment. We see a potential advantage in creating a prescriptive guidance providing specific examples as to when similarity would be accepted and when not. This could include examples of how much a molecule has to be chemically different to be considered non-similar.

	To reach consistency in the scientific assessment, the link shall be made to the notion of the same active substance in Article 10.2(b) of the Dir 2001/83/EC [3] and in the EMA/CHMP/QWP/104223/2015, Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances as suggested in the amendment. Any future equivalent guidance document relating to the evaluation of New Active Substance (NAS) status for biological substances would need to be considered as applicable. Proposed change: *- isomers, mixture of isomers, complexes, esters, ethers, salts, and derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue would be considered similar.* *To reach consistency in the scientific assessment, the link shall be made to the notion of the same active substance in the Article 10.2(b) of the Dir **2001/83EC** [4] and in the EMA/CHMP/QWP/104223/2015, Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances* [5]
38-47	The polynucleotides (in fact oligonucleotides) are mainly anti-sense or regulative RNAs (small interfering RNA = siRNA) with silencing or knock-out functions on gene expression. We suggest that any alteration of such a nucleotide molecule is defined as similar, as long as it binds to the same target sequence (a genomic region normally). Any altered kinetics of hybridization is irrelevant and should not be sufficient for non-similarity. Proposed change in red: We suggest the following amendments: *- synthetic polynucleotide substances, single or double-stranded, consisting of two or more nucleotides or derivatives thereof, where:* *- the difference in the sequence of the nucleotides or their derivatives does not prevent binding to the same target. Therefore, for antisense or interfering nucleotide substances, the addition, substitution, or deletion of nucleotide(s) not significantly affecting the hybridisation to the target would normally be considered similar* *- the difference in structure related to modifications of the ribose or deoxyribose backbone sugars or to the replacement of the backbone sugars by synthetic analogues would normally be considered similar.*

–Biological Medicinal products (BMP)

[3] Article 10.2(b) of the Dir 2**004/27/EC-** The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

[4] Article 10.2(b) of the Dir 2**001/83/EC-** The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

[5] Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/01/WC500199915.pdf

General comment:
The widely defined category of BMP is heterogeneous and includes very different groups of substances, such as biological proteins from natural sources (e.g. blood-derived proteins), vaccines, enzymes, hormones, cytokines, receptors, and monoclonal antibodies. They can be rather small (e.g. peptide hormones) or huge and complex (e.g. Factor VIII). With the help of recombinant gene technology, these substances can be produced but also modified. Moreover, there are also composed substances, which act as antagonists or inhibitors of active proteins. In a simplified and narrower consideration, BMPs are proteins (with only few exceptions, such as vaccines). Pure polysaccharides and lipopolysaccharides are used predominantly as drug delivery compounds rather than as active substances. There are few vaccines based on polysaccharides. Given the prominence of monoclonal antibodies in current development pipelines, it is important to address upfront the specificities of these products so that the proposed definition and approach remain valid overtime. Ideally vaccines should also have their own class (chapter).

Line	Proposed changes
54-58	In general, we support the text in lines 54-58. This opens up the possibility for amino acid sequence differences, as this is discussing functionality as opposed to identical sequences. However, the term “principal molecular structural feature” does not seem appropriate. It should be defined also via the function of the BMP by binding to a defined target, which is another protein, a receptor, or an epitope thereof. The specification of the target is also needed to define similarity. It has to be considered that a target protein consists of distinct epitopes and non-similarity may be defined if the new product binds to another epitope. Definitions are easier when just considering proteins (including glycoproteins, chemically conjugated proteins, and radiolabeled proteins, etc.). Some restriction shall apply. Other groups could be defined separately (vaccines, nucleotides). The activity or function of a protein drug requires the binding to a target molecule or part of a molecule. This is true for all categories of BMP. Enzymes bind to their substrates, cytokines and hormones to their receptors, antibodies to specific epitopes, and antagonists and inhibitors bind to specific target structures as well. Without binding there is no effect. It will be too complicated to subdivide the active substance into a “therapeutic moiety” and “structural elements”. This approach has a number of shortcomings in particular as many exceptions or intermediate situations exist and could lead to undue confusion. A common basic structure has to be assessed on the primary sequence of the protein in the binding region (functional part). For example a fragment binding to the same target as the intact antibody would then be considered similar. Small protein drugs, which are conjugated to increase the half-life (e.g. PEGylated proteins) have also be considered as similar (exceptions for those with “significant benefit”). The same applies to mutants introducing additional glycosylation sites to increase the half-life in vivo. Fusion proteins are more difficult. The fusion partner may have additional functions in vivo such as the Fc-moiety of immunoglobulins frequently used for fusion. Many other modifications exist which could be regarded as similar. Thus, we would suggest following strictly the criteria 1-4 listed on page 1-2). It is for the sponsor to justify to the CHMP that, despite compliance with 1-4, the new modified product is nevertheless superior and provides “significant benefits”.

	Proposed changes: The ~~principal~~ biologically relevant molecular ~~structural~~ features are those parts ~~the structural components~~ of an active substance that cause the binding to a target and define ~~are relevant for~~ the functionality of that substance. The ~~principal~~ molecular structure ~~structural features~~ may be composed of ~~a~~ therapeutically relevant regions ~~moiety or a therapeutic moiety~~ in combination with ~~an~~ additional structural elements. These ~~or~~ structural elements may also significantly contribute ~~contributing~~ to the biological activity ~~functionality~~ of the active substance. Such ~~an~~ additional structural elements can be chemically (covalently) conjugated, ~~fused or~~ linked or fused by ~~other~~ means of gene technology (gene fusion) to the therapeutically relevant region ~~moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids~~. Substances with such additional structural elements using similar technologies ~~methods~~ of ~~modification or~~ conjugation or fusion technology would normally result in similar substances. In the specific case of monoclonal antibodies, it should be understood that the biologically relevant part of the monoclonal antibody is primarily related to the complementary-determining regions (CDR) in the variable chains of the antibody, which specifically bind to their therapeutically relevant targets. However, the Fc-moieties of antibodies are not just "additional structural elements" as they bear several biological functions, too. Therefore, for justification of similarity, the monoclonal antibody has to be considered as whole.
67-68	Differences due to infidelity of transcription or translation are normally not detected well. Therefore we are of the opinion that this is not relevant, and we propose to remove these lines. This applies to all proteinaceous substances, including monoclonal antibodies. See proposed amendment to line 82-86. Proposed text (deletion): ~~*If the difference is due to infidelity of transcription or translation should normally be considered similar.*~~
69-73	In the case of post-translational events with different glycosylation patterns, the active substance may have a major change in terms of biological activity (efficacy or safety). This can be true where post-translational events are not extensive (e.g presence or absence of an amide or an acetyl group to amino acid side chains). Glycan modifications result in a heterogeneous population of molecules with a range of molecular structures. There isn't a single uniform population. The range for such structures in a biosimilar product, for example, must be within range for the same structural components of the reference product when these structures are deemed to be critical quality attributes affecting product efficacy, safety and/or stability. We proposed to change the wording to *"…. Different glycosylation patterns included in a range …"* Everything outside the range should be considered non-similar

	This applies to all proteinaceous substances, including monoclonal antibodies. See proposed amendment to line 82-86. Proposed text: *If the difference in structure between them is due to post-translational events (such as different glycosylation patterns included in a range) they should normally be considered similar. However, ~~the addition of~~ an extensive change of the glycan structure to the active moiety which results in the new glycosylation parameter being outside the range is considered non-similar ~~for example improving the binding capacity of the substance may result in a non-similar substance~~.*
74-75	The presence of an N-terminal methionine derived from a natural extraction process or rDNA encoding is the same amino acid. However any amino acid sequence differences between a biosimilar and a reference product are deemed to be non-similar products, due to the change in functionality of the protein. We propose to include this in the description. This applies to all proteinaceous substances, including monoclonal antibodies. See proposed amendment to line 82-86. Proposed text: *If the difference in the amino acid sequence is not major they 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 normally be considered similar. However, the addition of a structural element for example a conjugated amino acid sequence in rDNA derived proteins which results in a new substance being 'clinically superior' as defined in Article 3, 3 (d) of this Regulation ~~is for example a conjugated amino acid sequence in rDNA derived proteins~~ may be considered non-similar.*
82-86	This bullet point applies specifically to monoclonal antibodies and comes in addition to the first 3 bullet points which apply to all proteinaceous substances, including monoclonal antibodies. A definition of 'target epitope' or 'binding epitope' is needed to support common interpretation. Proposed text: *For the specific case of monoclonal antibodies and in addition to the above points, two monoclonal antibodies, binding to the same target epitope and having the same CDR sequence, would normally be considered as similar substances unless changes in other parts of the molecules are proven to show different functionalities or different pharmacokinetic behaviours.* *An epitope refers to a specific region of a target molecule, where an antibody binds. The epitope can be a short, continuous amino acid sequence on a target polypeptide (linear epitope) or a more complex region formed by the tertiary structure of a target polypeptide (conformational epitope). Post-translational modifications of a polypeptide, e.g.*

	glycosylation, can be part of an epitope, and even non-proteinaceous molecules can exhibit epitopes for antibodies.
88-89	Addressing the definition of similar polysaccharides, the specific characteristics of a polysaccharide do not solely depend on the nature of the saccharide units, but also on the substitution thereof (which could be interpreted as being included in the term "identical saccharide unit", but may not be), and on the type of the bond between such units. An alpha 1,4 glucan has different characteristics than a beta 1,3 glucan of the same length.) Proposed text: *If the substances have identical saccharide repeating units, (delete: even if) are identically linked and substituted, and only the number of units varies, they should normally be considered similar.*

Medicines for Europe

Medicines for Europe (formerly EGA) represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines for Europe, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and R&D sites in Europe, and invest up to 17% of their turnover in medical innovation.