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’ (Text with EEA relevance)

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(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[(1)], and in particular Article 8(4) thereof,

Whereas:

(1) Regulation (EC) No 141/2000 was adopted to promote research in the field of rare diseases. It offers undertakings that develop orphan medicinal products the prospect of obtaining market exclusivity for a certain number of years.

(2) Commission Regulation (EC) No 847/2000[(2)] provides a definition of the concept ‘similar medicinal product’, which includes specific cases defining what kind of products are to be regarded as similar for the purposes of the application of Article 8 of Regulation (EC) No 141/2000. That definition should be updated in the light of new scientific and technical knowledge, in particular, due to major developments in the field of biological medicines, and especially advanced therapy medicinal products, and in the light of experience gained with regard to the designation and regulation of orphan medicinal products.

(3) In addition, there is a need for a clear definition of the concept ‘principal molecular structural features’, which is used within the definition of the concept ‘similar active substance’, which is in turn used within the definition of the concept ‘similar medicinal product’. As regards the biological medicinal products, the definition of ‘principal molecular structural features’ shall capture certain molecular modifications significantly contributing to the functional characteristics of the active substance that would impact whether or not the products are considered as similar. However, for advanced therapy medicinal products the principal molecular structural features cannot be fully identified. Therefore, in the case of advanced therapy medicinal products the similarity between two active substances should be assessed on the basis of the biological and functional characteristics.

(4) The definition of ‘active substance’ should be deleted as Article 8(4) of Regulation (EC) No 141/2000 does not empower the Commission to define the term ‘active substance’.

Changes to legislation: *There are outstanding changes not yet made to Commission Regulation (EU) 2018/781. Any changes that have already been made to the legislation appear in the content and are referenced with annotations. (See end of Document for details) View outstanding changes*

The term 'active substance' is legally defined in Article 1(3)(a) of Directive 2001/83/EC of the European Parliament and of the Council[3] and the scope and purpose of Article 3(3) of Regulation (EC) No 847/2000 are related to the definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

(5) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

HAS ADOPTED THIS REGULATION:

Article 1

In Article 3(3) of Regulation (EC) No 847/2000, the introductory sentence and points (a), (b) and (c) are replaced by the following:

For the purposes of the application of Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products, the following definitions shall apply:

(a) deleted;

(b) "similar medicinal product" means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;

(c) "similar active substance" means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism. However, in the case of advanced therapy medicinal products, for which the principal molecular structural features cannot be fully defined, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics.

For the purpose of application of point (c) above, the following applies for:

(1) Chemical medicinal products

The principal molecular structural features are the relevant structural components of an active substance. They can be the whole or part of the molecule. Whether the principal molecular structural features are the same between two or more molecules will be identified by comparison of their structures.

(1.1) 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, shall be considered similar.

(1.2) Synthetic polynucleotide substances, single or double stranded, consisting of two or more distinct nucleotides where:

— the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives is not major, shall be considered similar. Therefore for antisense or interfering nucleotide substances, addition, substitution or deletion of a nucleotide not significantly affecting the kinetics of hybridisation to the target shall 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 shall normally result in substances being considered

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similar. For antisense or interfering nucleotide substances, changes in the (deoxy-)ribose not significantly affecting the kinetics of hybridisation to the target would normally be considered similar.

(2) Biological medicinal products (other than advanced therapy medicinal products)

The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics 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(s) significantly contributing to the functional characteristics of the active substance.

Such an additional structural element(s) can be conjugated, fused or linked by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids. Substances with structural elements for which similar methods of modification or conjugation technology are used shall normally result in similar substances.

Biological active substances that differ from the original biological substance only with respect to minor changes in the molecular structure shall be considered similar.

(2.1) Proteinaceous substances:

If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) substances shall normally be considered similar. However, exceptionally some post-translational modifications may result in a non-similar substance, if there is significant effect on the functional characteristics of the substance.

If the difference in the amino acid sequence is not major, substances shall 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) shall normally be considered similar. However, the addition of a structural element may result in substances being considered non-similar if this significantly affects the functional characteristics of the substance.

Monoclonal antibodies binding to the same target epitope shall normally be considered similar. However, two monoclonal antibody conjugates or fusion proteins could be determined to be non-similar if either the Complementary Determining Region sequences of the antibody or the additional structural element of the conjugated monoclonal antibody were different.

(2.2) Polysaccharide substances:

If the substances have identical saccharide repeating units, even if the number of units varies, they shall 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.

(3) Advanced Therapy Medicinal Products (ATMPs)

(3.1) Cell-based ATMPs: Two related cell-based medicinal products are not similar if: