



EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicines: policy, authorisation and monitoring

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

CONSULTATION DOCUMENT

The purpose of this consultation is to collect views, relevant evidence and information from stakeholders to help the European Commission develop its thinking in this area.

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

INTRODUCTION

Regulation (EC) No 141/2000 on orphan medicinal products was developed to promote the research, development and marketing of medicinal products for rare diseases. The Regulation calls on the Commission to adopt the necessary provisions for implementation and definitions.

After 15 years of implementation of the orphan legislation, the Commission is currently launching initiatives to improve the implementation of the regulatory framework with a view to ensure timely access to medicinal products. In this context, the Commission has decided to launch a targeted review of Commission Regulation (EC) No 847/2000 on the concept of similarity. In parallel, the Commission is also finalising the revision of the 2003 Communication on Regulation (EC) No 141/2000 on orphan medicinal products (2003/C 178/02) which will be replaced by a notice.

The cornerstone of the orphan rules is the principle of market exclusivity. When a marketing authorisation for an orphan medicinal products 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

Article 3 paragraph (3) of Commission Regulation 847/2000 provides a definition of 'similar medicinal products' and a number of examples defining what kind of products are to be regarded as similar for the purposes of the application of the incentives provided under Regulation 141/2000. The definitions of Regulation 847/2000 require adaption to technical progress due to major developments in the field of biological medicines including advanced therapy medicinal products.

Stakeholders are invited to provide their views on the changes suggested to Article 3 of Commission Regulation (EC) No 847/2000.

PROPOSALS FOR CHANGE

Removal of the definition of active substance

1
2 Article 3 (3)(a) of Commission Regulation (EC) No 847/2000 should be repealed as
3 Article 8(4) of REGULATION (EC) No 141/2000 does not empower the Commission
4 to define the term "active substance". Article 8(1) and 8(3) of REGULATION (EC)
5 No 141/2000 do not use the term "active substance" but contain the wordings "*for the*
6 *same therapeutic indication, in respect of a similar medicinal product*", "*for the same*
7 *therapeutic indication to a similar medicinal product*" and "*more effective or*
8 *otherwise clinically superior*". The term "active substance" is legally defined in
9 Article 1 (3) (a) of Directive 2001/83/EC¹ and the scope and purpose of Article 3(3)
10 of Commission Regulation (EC) No 847/2000 are related to the definitions of the
11 concepts 'similar medicinal product' and 'clinical superiority' (Article 1 of
12 Commission Regulation (EC) No 847/2000).

Definition of similar active substance

13 As stated in Commission Regulation 847/2000, 'similar active substance' means an
14 identical active substance, or an active substance with the same principal molecular
15 structural features (but not necessarily all of the same molecular structural features) and
16 which acts via the same mechanism.

17 This includes:

18 – Chemical medicinal products

19 *The current definition of similar active substance raises numerous questions from*
20 *stakeholders in relation to the meaning of the principal molecular structural features.*
21 *Moreover, the examples to define what products are considered similar do not take into*
22 *account the existence of ether and co-valent derivatives. Over the years, more orphan*
23 *medicinal products have been developed and authorised. It is therefore crucial to bring*
24 *certainty on the application of the concept of similarity taking into account new*
25 *pharmaceutical developments. To this end, it is proposed to provide a definition of the*
26 *principal molecular structural features, to add a reference to ether and to remove the*
27 *reference to non-covalent derivatives of the original active substance to take into*
28 *consideration the covalent and non-covalent derivatives.*

29 *The following text is proposed for revision and possible comments by stakeholders:*

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

34 - isomers, mixture of isomers, complexes, esters, ethers, salts, and derivatives of
35 the original active substance, or an active substance that differs from the original
36 active substance only with respect to minor changes in the molecular structure,
37 such as a structural analogue would be considered similar.

¹ DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6
November 2001 on the Community code relating to medicinal products for human use, OJ L 311,
28.11.2001, p. 67.

- 38 - synthetic polynucleotide substances consisting of two or more distinct nucleotides
39 where:
- 40 - the difference in the nucleotide sequence of the purine and pyrimidine
41 bases or their derivatives is not major. Therefore for antisense substances,
42 the addition or deletion of nucleotide(s) not significantly affecting the
43 kinetics of hybridisation to the target would normally be considered
44 similar
- 45 - the difference in structure between them relates to modifications to the
46 ribose or deoxyribose sugar backbone or to the replacement of the
47 backbone by synthetic analogues would normally be considered similar.
- 48 – Biological Medicinal products
- 49 *It is proposed to update the examples to take into account new technological*
50 *developments such as conjugation (conjugated coagulation factors), monoclonal*
51 *antibody technology, cell-based medicinal products and gene therapy medicinal*
52 *products.*
- 53 *The following text is proposed for revision and possible comments by stakeholders:*
- 54 The principal molecular structural features are the structural components of an active
55 substance that are relevant for the functionality of that substance. The principal
56 molecular structural features may be composed of a therapeutic moiety or a therapeutic
57 moiety in combination with an additional structural element or structural elements
58 significantly contributing to the functionality of the active substance.
- 59 Such an additional structural element can be conjugated, fused or linked by other means
60 to the therapeutic moiety or can be an extension of the therapeutic moiety protein
61 backbone by additional amino acids.
- 62 Substances with structural elements using similar methods of modification or
63 conjugation technology would normally result in similar substances.
- 64 Biological active substances that differ from the original biological substance only with
65 respect to minor changes in the molecular structure such as:
- 66 - proteinaceous substances:
- 67 - If the difference is due to infidelity of transcription or translation should
68 normally be considered similar.
- 69 - If the difference in structure between them is due to post-translational
70 events (such as different glycosylation patterns) should be normally
71 considered similar. However, the addition of an extensive glycan structure
72 to the active moiety for example improving the binding capacity of the
73 substance may result in a non-similar substance.
- 74 - If the difference in the amino acid sequence is not major should normally
75 be considered similar. Therefore, two pharmacologically related protein
76 substances of the same group for example having differences related to
77 e.g. n-terminal methionine, naturally extracted versus rDNA derived
78 proteins (or other minor variants) would normally be considered similar.
79 However, the addition of a structural element which is for example a
80 conjugated amino acid sequence in rDNA derived proteins may be
81 considered non-similar.

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

87 - polysaccharide substances:

88 - If the substances have identical saccharide repeating units, even if the
89 number of units varies should normally be considered similar.

90 - A conjugated polysaccharide vaccine compared to a non-conjugated
91 polysaccharide vaccine containing the same antigen is considered a non-
92 similar substance. Two conjugated vaccines derived from the same
93 antigen and using similar methods of modification or conjugation
94 technology would be considered similar substances.

95 – Radiopharmaceutical medicinal products

96 The same radiopharmaceutical active substance, or one differing from the original in
97 radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism
98 linking the molecule and radionuclide provided that it acts via the same mechanism.

99 An active substance is not considered similar in cases of:

100 (aa) ATMPs for which principal molecular structural features cannot be fully defined and
101 the similarity between two active substances needs to be assessed on the basis of
102 biological and functional characteristics. In particular the following considerations apply
103 in order to conclude whether two related cell-based medicinal products are not similar:

104 - there are differences in starting materials or the final composition of the product
105 which have significant impact on the biological characteristics and/or activity
106 relevant for the intended therapeutic effect of the product. The different source of
107 the starting materials (e.g. as in the case of autologous ATMPs) is not sufficient
108 to support a claim that two products are non-similar; or

109 - there are differences in the manufacturing technology having a significant impact
110 on the biological characteristics and/or activity relevant for the intended
111 therapeutic effect of the product.

112 (bb) Two gene therapy medicinal products when there are differences in the therapeutic
113 sequence, viral vector, transfer system or regulatory sequences that significantly affect
114 the biological characteristics and/or activity relevant for the intended therapeutic effect
115 of the product. Minor differences in the therapeutic sequence without a significant impact
116 on the intended therapeutic effect are not sufficient to support the claim that two gene
117 therapy medicinal products are non-similar.

118 (cc) Genetically modified cells. The considerations under (aa) and (bb) apply.

119