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Orphan medicines. The European Commission updates the definition of 'similar medicinal product'

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The continuous advance in scientific research and technical knowledge in the pharmaceutical industry make it very important to put in place continuous updates of the legal framework regulating medicinal products so that companies are able to conduct their business at a level playing field and patients' interests are protected. To that end, on 29 May 2018 the European Commission has adopted Commission Regulation (EU) 2018/781 amending Regulation (EC) No 847/2000, laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts of 'similar medicinal product' and 'clinical superiority', as regards the definition of 'similar medicinal product'[1].

Regulation (EC) No 847/2000[2] defines a 'similar medicinal product' as a '… *medicinal product containing a similar active substance o*[r] *substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication*…'[3]. It also specifies that 'similar active substance' means '… *an identicial 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*…'[4]. Such definitions are supplied for the purposes of the implementation of Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products[5].

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[1] 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', OJEU L 132 of 30.05.2018.

[2] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority', OJEU L 103 of 28.04.2000.

[3] Article 3, paragraph 3(b).

[4] Article 3, paragraph 3(c).

[5] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJEU L 18 of 22.01.2000. According to its Article 8, '… 1. *Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products(7), and without prejudice to intellectual property law or any other provision of Community law, the Community 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.*

2. This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.

3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

Orphan medicinal products are used to treat rare diseases and are so called because the pharmaceutical industry would, in the absence of a friendly regulatory environment, have little financial interest in developing and marketing products intended for only very small numbers of patients suffering from rare conditions. Regulation (EC) No 141/2000 on orphan medicinal products was introduced with the aim of stimulating research and development and bringing to the market appropriate medications so that patients suffering from rare conditions would have the same quality of treatment as other patients. The Regulation establishes a centralised procedure at EMA level for the designation of orphan medicines and puts in place incentives for their research, development and commercialization. Pharmaceutical companies can benefit from such incentives as fee reductions for regulatory activities[6], scientific assistance for marketing authorisation and the possibility of an EU marketing authorisation with a 10-year market exclusivity period.

In the light of new scientific and technical knowledge, in particular, in the field of biological medicines and advanced therapies, and in the light of the experience gained in the past with regard to the designation and regulation of orphan medicinal products, the Commission found that the definition of 'similar medicinal product' provided in Regulation (EC) No 847/2000 needed to be updated. Moreover, the need was felt for a clear definition of the concept of 'principal molecular structural features', which is used within the definition of 'similar active substance', which is in turn used within the definition of 'similar medicinal product'.

The new Regulation states that the principal molecular structural features are the relevant structural components of an active substance. For chemical medicinal products, where the principal molecular structural features are the same between two or more molecules, they will be identified by comparison of such structures. With regard to 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 have an impact, whether or not the products are considered as similar[7]. However,

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(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.
4. The Commission shall adopt definitions of "similar medicinal product" and "clinical superiority" in the form of an implementing Regulation in accordance with the procedure laid down in Article 72 of Regulation (EEC) No 2309/93.
5. The Commission shall draw up detailed guidelines for the application of this Article in consultation with the Member States, the Agency and interested parties…'.

[6] This includes reduced fees for protocol assistance, marketing-authorisation applications, inspections before authorisation, applications for changes to marketing authorisations made after approval, and reduced annual fees.

[7] Article 1, Regulation (EU) 2018/781: '… *The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of*

for advanced therapy medicinal products the principal molecular structural features cannot be fully identified. Therefore, in such cases the similarity between two active substances should be assessed on the basis of their biological and functional characteristics.

The new Regulation also deletes the definition of 'active substance' provided in Regulation (EC) No 847/2000[8], since Article 8(4) of Regulation (EC) No 141/2000 does not empower the Commission to define such notion. This term is legally defined in Article 1(3)(a) of Directive 2001/83/EC[9] whilst 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'.

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…'.

[8] Article 3, paragraph 3(a): '… *"active substance" means a substance with physiological or pharmacological activity*…'.

[9] 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, OJEU L 311 of 28.11.2001.