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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'

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Article 1

Purpose

This Regulation lays down factors to be considered when implementing Article 3 of Regulation (EC) No 141/2000 on orphan medicinal products and establishes definitions of 'similar medicinal product' and 'clinical superiority' for the purposes of implementing Article 8 of the abovementioned Regulation. It is intended to assist potential sponsors, the Committee for Orphan Medicinal Products, and competent authorities in the interpretation of Regulation (EC) No 141/2000.

Article 2

Criteria for designation

1. *Prevalence of a condition in the Community*

For the purpose of establishing, pursuant to the first subparagraph of Article 3(1)(a) of Regulation (EC) No 141/2000, that a medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 000 persons in the Community, the following specific rules shall apply and the documentation listed below shall be provided in accordance with the guidance drawn up pursuant to Article 5(3) of Regulation (EC) No 141/2000:

(a) the documentation shall include appended authoritative references which demonstrate that the disease or conditions for which the medicinal product would be administered, affects not more than five in 10 000 persons in the Community at the time at which the application for designation is submitted, where these are available;

(b) the data shall include appropriate details on the condition intended to be treated and a justification of the life-threatening or chronically debilitating nature of the condition supported by scientific or medical references;

(c) the documentation submitted by the sponsor shall include or refer to a review of the relevant scientific literature, and shall provide information from relevant databases in the Community, where these are available. Where no database in the Community is available, reference may be made to databases available in third countries, provided the appropriate extrapolations are made;

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(d) where a disease or condition has been considered within the framework of other Community activities on rare diseases, this information shall be provided. In the case of diseases or conditions included in projects financially supported by the Community in order to improve information on rare diseases, a relevant extract from this information, including in particular, details of the prevalence of the disease or condition in question, shall be provided.

2. *Potential for return on investment*

For the purpose of establishing, pursuant to the second subparagraph of Article 3(1)(a) of Regulation (EC) No 141/2000, that a medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community, and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necesary investment, the following specific rules shall apply and the appropriate documentation shall be provided in accordance with the guidance drawn up pursuant to Article 5(3) of Regulation (EC) No 141/2000:

(a) the data shall include appropriate details on the condition intended to be treated and a justification of the life-threatening or seriously debilitating or serious and chronic nature of the condition supported by scientific or medical references;

(b) the documentation submitted by the sponsor shall include data on all costs that the sponsor has incurred in the course of developing the medicinal product;

(c) the documentation provided shall include details of any grants, tax incentives or other cost recovery provisions received either within the Community or in third countries;

(d) in cases where the medicinal product is already authorised for any indication or where the medicinal product is under investigation for one or more other indications, a clear explanation of and justification for the method that is used to apportion the development costs among the various indications shall be provided;

(e) a statement of and justification for all development costs that the sponsor expects to incur after the submission of the application for designation shall be provided;

(f) a statement of and justification for all production and marketing costs that the sponsor has incurred in the past and expects to incur during the first 10 years that the medicinal product is authorised shall be provided;

(g) an estimate and justification for the expected revenues from sales of the medicinal product in the Community during the first 10 years after authorisation;

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(h) all cost and revenue data shall be determined in accordance with generally accepted accounting practices and shall be certified by a registered accountant in the Community;

(i) the documentation provided shall include information on the prevalence and incidence in the Community of the condition for which the medicinal product would be administered at the time at which the application for designation is submitted.

3. *Existence of other methods of diagnosis, prevention or treatment*

An application for designation of a medicinal product as an orphan medicinal product may be submitted in accordance with either paragraph 1 or paragraph 2 of this Article. Irrespective of whether an application for designation is submitted in accordance with paragraph 1 or 2, the sponsor must additionally establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition.

For the purpose of establishing, pursuant to Article 3(1)(b) of Regulation (EC) No 141/2000 that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition, the following rules shall apply:

(a) details of any existing diagnosis, prevention or treatment methods of the condition in question that have been authorised in the Community shall be provided, making reference to scientific and medical literature or other relevant information. These may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community;

(b) either a justification as to why the methods referred to in paragraph (a) are not considered satisfactory;

or

(c) a justification for the assumption that the medicinal product for which designation is sought will be of significant benefit to those affected by the condition.

4. *General provisions*

(a) A sponsor applying for designation of a medicinal product as an orphan medicinal product shall apply for designation at any stage of the development of the medicinal product before the application for marketing authorisation is made. An application for designation may however be submitted for a new therapeutic indication for an already authorised medicinal product. In this case, the marketing authorisation holder shall apply for a separate marketing authorisation which will cover only the orphan indication(s).

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(b) More than one sponsor may obtain designation as an orphan medicinal product for the same medicinal product intended to prevent, treat or diagnose the same disease or condition, provided that a complete application for designation as laid down by the guidelines specified in Article 5(3) is submitted in each case.

(c) Where a medicinal product is designated by the Committee for Orphan Medicinal Products reference to the criteria for designation will be made either to Article 2(1) or to Article 2(2) of this Regulation.

Article 3

Definitions

1. The definitions in Article 2 of Regulation (EC) No 141/2000 apply to those terms when used in this Regulation:

— 'substance' means a substance used in the manufacture of a medicinal product for human use as defined in Article 1 of Directive 65/65/EEC.

2. For the purposes of the implementation of Article 3 of Regulation (EC) No 141/2000 on orphan medicinal products, the following definition shall apply:

— 'significant benefit' means a clinically relevant advantage or a major contribution to patient care.

3. ►**M1** 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:

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(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 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.

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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:

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

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— there are differences in the manufacturing technology having a significant impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.

(3.2) Gene therapy medicinal products: Two gene therapy medicinal products shall not be considered similar when there are differences in the therapeutic sequence, viral vector, transfer system, regulatory sequences or manufacturing technology that significantly affect the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.

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.

(3.3) Genetically modified cells. The considerations under (3.1) and (3.2) apply.

(4) Radiopharmaceutical medicinal products

The same radiopharmaceutical active substance, or one differing from the original in radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism linking the molecule and radionuclide provided that it acts via the same mechanism shall be considered similar substances; ◄

(d) ‘clinically superior’ means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:

(1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case, the methodological approach should be justified;

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(2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary;

or

(3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.

Article 4

Entry into force

This Regulation shall enter into force on the day following its adoption by the Commission and shall apply from the same day.

This Regulation shall be binding in its entirety and directly applicable in all Member States.