EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

PHARM 703

PHARMACEUTICAL COMMITTEE
28 April 2016

Subject: Orphan medicinal products

Agenda item 2ii

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

The purpose of this paper is to seek the views of the Committee on two documents that aim to streamline the regulatory framework on orphan medicinal products.

1. Commission notice on orphan medicinal products

The Commission would like to summarise the outcome of the public consultation on the *"Commission notice on the application of Article 3, 5 and 7 of Regulation (EC) no 141/2000 on orphan medicinal products"* and seeks the views of the group concerning the proposals for which diverging opinions have been expressed (see below). All non-controversial comments will be included in the revised version of the notice, which is attached to this paper.

Overall, all respondents welcomed the Commission's proposal to review the 2003 Communication, which would make orphan designation a more effective tool for encouraging research and development of medicinal products for rare diseases. Most respondents also supported the maintenance of the main Regulation in its current form but asked for further clarity and guidance on the implementation of the legislation through the notice or other instruments. Depending of the final proposals, some suggestions may also be integrated in the Commission Regulation (EC) No 847/2000.

Some proposals of the respondents cannot be addressed in the forthcoming notice and are therefore presented in Annex 2 to this paper. This includes improving the access to orphan medicinal products, reviewing the conditional marketing authorisation, reviewing the market exclusivity after five years of authorisation or reviewing the functioning of the main Regulation on orphan.

The following consultation items were presented during the public consultation:

Clarification of the definition of "significant benefit"

All respondents welcomed the proposal to clarify how the sponsor needs to demonstrate a significant benefit over satisfactory methods of treatment. Some respondents asked to be more stringent while others asked more flexibility. Respondents expressed diverging opinions on the reference to medicines prepared in a (hospital) pharmacy as a satisfactory method of treatment.
Some respondents supported the Commission's proposal to consider hospital preparations. According to one respondent, whether medicinal products prepared in a hospital pharmacy should be considered as a satisfactory treatment depends on the ease of preparation of such products and evidence that this is a general practice in the EU, i.e. if a centrally registered orphan product does not enter the market, patients in the EU will still be guaranteed treatment with the pharmacy preparation. Respondents also indicated that there are cases where an accessible magistral preparation from a sponsor is marketed as an orphan medicinal product may no longer be accessible for patients due to market exclusivity and often the high price. One respondent believed that hospital preparation should be considered in the scope if its safety is demonstrated. Another respondent considered that 10 years of market exclusivity is excessive when a hospital preparation exists, as there are no costs for the development of such products.
On the other hand, some respondents proposed that hospital preparations should not be taken into account as their existence should not remove the incentive to the development of industrially manufactured orphans which are subject to a rigorous process for demonstrating quality, safety and efficacy in the interest of public health. Products prepared in pharmacy are not authorised and do not require any quality, safety and efficacy data and it is not possible to trace if these products are available across European hospitals.

Encouraging the development of orphan medicinal products for communicable diseases (e.g. Ebola)

Most respondents welcomed the proposal to extend orphan designations to the treatment of communicable diseases which could rapidly become a public health threat.

Simplifying the procedure for the reassessment of orphan criteria when two authorisation application procedures are pending in parallel for two orphan medicinal products

The majority of respondents welcomed the suggestion to simplify the reassessment of the criteria. The Commission proposed that the sponsor of the second product should not demonstrate the significant benefit over a medicine assessed positively by EMA only one or two months before. Nevertheless, many respondents believed that the flexibility of 2 months between two applications is not sufficient to lead to a real improvement. In such short timelines, demonstration of significant benefit over the first product could only be supported by indirect comparisons, as appropriate clinical data are not readily available to the second applicant. Most respondents (mainly industry) suggested that a sponsor should not provide evidence of significant benefit over a medicine that has obtained a marketing authorisation after his marketing authorisation has been submitted/validated. On the other

hand, some respondents would be stricter and would require the comparison in all cases of one product over the other. The comparisons with the more-recently authorised products is required to be consistent with other procedures e.g. status of new active substances or major contribution to patient care in the CMA.

Introducing the reassessment of the orphan criteria for a new subset of the condition when a sponsor extends the use of its product after marketing authorisation

Respondents expressed diverging views on the proposal to re-assess the criteria. Some respondents supported the proposal because the orphan criteria should be assessed for any extension, or variation of indication in the same way as for the initial authorisation. This proposal would ensure equal treatment between the sponsors. On the other hand, many respondents believed that this additional requirement, which is not linked to any additional incentives(no additional market exclusivity), would discourage development in the area of rare diseases and create delays in the approval of new indications. A formal review of the orphan criteria every time a marketing authorisation holder extends the therapeutic indication within the same orphan condition might discourage development in the area of rare diseases. This would add an additional hurdle to keep the orphan incentive in a situation where since the granting of the first marketing authorisation, market exclusivity already exists. If the company does not have the certainty that their proposed new indication would benefit from market exclusivity they might refrain from further developing the product in that indication. They believe that this might also promote off-label use rather than stimulating the authorisation of new indication. This could lead to a delay in the application and access to patients until the company is reassured that enough data has been generated to justify significant benefit in the new indication.

Clarifications on processing the transfer of orphan designations between sponsors

All respondents welcomed the proposal

2. Review of Commission Regulation (EC) No 847/2000 on the concept of similarity

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 (commonly known as the market exclusivity's incentive under the orphan legislation). Commission Regulation (EC) No 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[1].

[1] REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products

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.

The Commission services have asked the Agency for technical input on this question. The contribution developed by the CHMP and the CAT is attached.

Member States are invited to provide their views on the technical questions addressed by the CHMP/CAT document.

Action to be taken:
For discussion

Annex 1

JOINT CHMP – CAT DOCUMENT

Amendment of Article 3 paragraph (3) of Commission Regulation (EC) No 847/2000

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

(a) 'active substance' means a substance with metabolic, immunological or pharmacological activity or for tissue engineered products with properties for the regeneration, replacement or repair of a human tissue;

(b) 'similar medicinal product' means a medicinal product containing a similar active substance of 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, with exception of products covered under d).

This includes:

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. Sameness of principal molecular structural features between two or more molecules will be identified by comparison of their structures.

- 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.
- synthetic polynucleotide substances 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. Therefore for antisense substances, the addition or deletion of nucleotide(s) not significantly affecting the kinetics of hybridisation to the target would normally be considered similar
    - the difference in structure between them relates to modifications to the ribose or deoxyribose sugar backbone or to the replacement of the backbone by synthetic analogues would normally be considered similar.

Biological Medicinal products

The principal molecular structural features are the structural components of an active substance that are relevant for the functionality 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 or structural elements significantly contributing to the functionality of the active substance.

Such an additional structural element 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 using similar methods of modification or conjugation technology would 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 such as:

- proteinaceous substances:
    - If the difference is due to infidelity of transcription or translation should normally be considered similar.
    - If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) should be normally considered similar. However, the addition of an extensive glycan structure to the active moiety for example improving the binding capacity of the substance may result in a non-similar substance.
    - If the difference in the amino acid sequence is not major 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 which is for example a conjugated amino acid sequence in rDNA derived proteins may be considered non-similar.
    - Monoclonal antibodies binding to the same target epitope would normally be considered similar. However, two monoclonal antibody conjugates or fusion proteins would be determined to be non-similar if either the CDR sequences of the antibody or the additional structural element of the conjugated monoclonal antibody were different.
- polysaccharide substances:
    - If the substances have identical saccharide repeating units, even if the number of units varies should 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. Two conjugated vaccines derived from the same antigen and using similar methods of modification or conjugation technology would be considered similar substances.

Advanced Therapy Medicinal Products

(d) For ATMPs for which principal molecular structural features cannot be fully defined, the similarity between two active substances should be assessed on the basis of biological and functional characteristics. In particular the following considerations apply:

(1) Two related cell-based medicinal products are not similar where:

- there are differences in starting materials or the final composition of the product which have significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect 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
- there are differences in the manufacturing technology having a significant impact on the biological characteristics and/or activity relevant for the intended therapeutic effect of the product

(2) Two gene therapy medicinal products are not similar when there are differences in the therapeutic sequence, viral vector, transfer system or regulatory sequences that significantly affect the biological characteristics and/or activity relevant for the intended therapeutic effect of the product.

Minor 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) For genetically modified cells, the considerations under (1) and (2) apply.

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.

Annex 2
Other comments/suggestions from the public consultation on the notice

Some proposals of the respondents cannot be addressed in the forthcoming notice. These comments may feed the reflections and initiatives of the Commission in the coming years (e.g. the review of the Commission Regulation on similarity or the Commission Regulation on the conditional marketing authorisation):
Some respondents asked the Commission to:
- Totally review the functioning and application of the orphan Regulation and ensure that proposals go further than the proposed notice;
- Consider measures to improve access to orphan medicinal products, facilitate joint procurement, match the emerging HTA processes. Various recent studies have highlighted the growing influx of new orphan medicinal products with limited added-value for the patients and an increasingly greater budgetary impact. Moreover, marketing authorisations for similar medicines for various rare diseases and non-orphan disease may raise the question if the number of patients served by all indications is above the prevalence of 5 in 10,000 patients in the EU;
- Review the conditional marketing authorisation (CMA) for orphan medicinal products. The CMA pathway is vital for expedited pathway for patient access to innovative medicines in areas of unmet medical needs. Data submitted to fulfil the "unmet medical need" in the context of the CMA should be sufficient to demonstrate significant benefit for the orphan status. Re-assessment of the significant benefit at the time of the fulfilment of the specific obligations should be introduced in the legislation. (post-authorisation reassessment);
- Clarify the non-acceptability of sub-setting based on biomarkers notably to avoid divergence on the use of the term 'condition' with the paediatric committee;
- Reinforce the review of market exclusivity after five years (Article 8(2)). The procedure of review as adopted in Communication C(2008)4051 places the burden of proof with the Member State who often lack overview;
- Review the concept of similarity to avoid ever-greening strategy for blocking generic competition , review the definition of what constitute a similar product. If new pharmaceutical forms of authorised product are afforded 10 years of market exclusivity, other existing formulations of the same active substance cannot gain a marketing authorisation. It is proposed to give the orphan designation to the active substance, the pharmaceutical form and to the indication;
- Earlier and stronger coordination between the COMP and CHMP throughout the marketing authorisation process;
- Investigate the possibility to explore orphan designation on the basis of the investment criterion for example for re-purposing useful medicines in common disease areas;
- Prioritise the development of adult oncology medicines for paediatric population and consider new incentives.