



EURORDIS Answer to the European Commission Consultation on:

Concept of ‘Similar Medicinal Product’ in the context of the orphan legislation:

Adaptation to technical progress

EURORDIS is welcoming the Consultation on the concept of ‘similarity’ in the context of the orphan legislation and is hereby providing some comments.

EURORDIS acknowledges the necessity of reviewing the implementation of the regulatory framework in relation to the concept of ‘similarity’ and updating the Commission Regulation (EC) No 847/2000 in light of the technical progress which have happened over the 16 past years and takes note that this review only targets the concept of ‘similarity’.

Taking into account the 3 criteria underlying the concept of similarity, namely Principal Molecular Structural Features, Mechanism of Action and Therapeutic indication, EURORDIS understands that the proposed changes are addressing the first one: Principal Molecular Structural Features (PMSF), and is of the opinion that a clear and unequivocal definition of similarity with regards to PMSF is of utmost importance.

Major developments in the biological fields probably allow nowadays -much more than when the Regulation came into force- to distinguish one product from another on solid scientific grounds. This gained scientific knowledge should therefore be used to a broad extent in order to avoid labelling as similar, products that are in reality not, upon the current state-of-the-art. Practically speaking, this translates probably into a more detailed and in depth assessment of the different components of an ATMP.

The notion of similarity is dynamic and it will evolve over time along with the product’s development cycle and with the newly generated data on safety and efficacy. At early stage, some features of the product could reveal an impact on the safety profile, while some structural modifications may demonstrate later on, an impact on efficacy which would drive the benefit for the patients. Thus, the understanding of the potential functionalities may vary over time and impact on the assessment of similarity or non-similarity of some structural features.

The increased level of detail in the definition of PMSF is likely to yield greater numbers of non-similar products than previously. This fact is absolutely relevant from the patients’ perspective as long as the therapeutic effect for each of these products is demonstrated. The crucial point is the identification of functional elements in a particular product which are linked to the product’s efficacy in the broader patient population or in a targeted sub-population.

In the context of the orphan legislation, more products labelled as non-similar would likely lead to more products coming to the market (with or without the maintenance of their orphan status) and therefore would represent more therapeutic alternatives for patients.

On the other hand, products labelled as similar would be ‘more strictly similar’ and would likely be less able to demonstrate that they are safer, more effective or otherwise clinically superior. This would translate in less opportunity for a new similar product to breach the market exclusivity of another product, reinforcing the concept of market exclusivity at the same time.

In our opinion, the proposed changes are therefore calling for more innovation from the developers' side, and the existence of therapeutic alternatives might help mitigate the impact on civil society, as more competition will likely translate into lower prices of those treatments.

Considering this evolution of the legislation, the most challenging aspect would probably lie in the necessity to demonstrate significant benefit of these non-similar products when assessing the maintenance of orphan status at the time of marketing authorization, which will be increasingly difficult when some medical areas are becoming crowded. Our position on the matter has been elaborated in our answer to the previous consultation on the Notice, where we suggested a reconsideration of the notion of 'significant benefit', so to approach it more globally [http://ec.europa.eu/health/files/orphanmp/2015_11_pc_orphanmp/replies/2015_11_pc_orphans_eurordis.pdf].

Predictability is a key component of therapeutic development for pharmaceutical companies. It will be crucial that the issue of similarity be addressed as early as possible in a dialogue between the developers and the regulators. This exchange would inform not only the question of similarity or non-similarity and therefore the potential for the product to access the market, but also to anticipate of the issue of significant benefit for a non-similar product.

At least, a two-step dialogue would be needed, one very early in the development and one (or more) later on as long as the development progresses and that new data are generated, which may then lead to a re-adjustment of the assessment as explained above. Early dialogues, such as the one taking place within the PRIME initiative or when a company is seeking Scientific Advice at the EMA should consider the relevance of discussing the question of similarity, with the presence of the relevant experts from CHMP, CAT or invited experts.

Technical advances are in constant evolution and EURORDIS is of the opinion that definitions have to be dynamic and have to leave flexibility in the implementation of the Regulation, so that to be able to adapt regularly to the progresses and not having to re-open the text of the Regulation each time a new scientific step is made.

An area that would probably benefit from additional considerations with regards to technical advances and which is not at all touched upon in the present consultation is the field of medical devices and more precisely of combined products, which is likely to take more and more space in the near future of the therapeutic development. We are referring here for example to the case of Vantobra/TobiPodhaler (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002633/s_mops/Positive/human_smop_000685.jsp&mid=WC0b01ac058001d127). This type of situation is likely to happen more often and would benefit from a better and clearer guidance.

In the case of ATMPs, we cannot exclude that progresses in nanotechnology or 3D printing, for example, would bring to the therapeutic development field some combined product with a 'small device' element embedded into a cell or a tissue.

Some additional line-to-line comments are presented on next page.

Line-to-line comments:

Line 1-12: This paragraph is quite difficult to understand and this might undermine the understanding of the purpose of the revision and of the Regulation in itself. We feel that there is a need of alignment between the legislative documents and a harmonisation of the wording, such as:

The Commission is empowered by Article 8(4) of REGULATION (EC) No 141/2000 to define the concepts 'similar medicinal product' and 'clinical superiority'. These definition were laid down in Article 1 of Commission Regulation (EC) No 847/2000) and the scope and purpose of Art. 3(3) are related to those definitions. However, Reg. (EC) No 141/2000 does not empower the Commission to define the term "active substance". Consequently Article 3 (3)(a) of Commission Regulation (EC) No 847/2000, defining 'active substance', should be repealed. The term "active substance" is legally defined in Article 1 (3) (a) of Directive 2001/83/EC. 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 same therapeutic indication, in respect of a similar medicinal product", "for the same therapeutic indication to a similar medicinal product" and "more effective or otherwise clinically superior".

Line 18-94: We think that 'Pegylated components' should be mentioned somewhere in the text and that guidance should be given: for example, are Pegylated moieties of different molecular weight e.g. 30 kDa compared to 60 kDa, considered similar or not?

Line 66 – 86: About Proteinaceous substances, we would like to draw attention on 'starting materials', for instance the nature of the cell line that is being used to generate the recombinant protein. We know that hamster cells lead to different glycosylation of recombinant proteins compared to human cells. This might have implications for immunogenicity of the recombinant protein. This topic is worthwhile to discuss.

Line 104-108: We would like to find in this paragraph, further clarification on defining 'starting materials' and in particular the mention of 'e.g. as in the case of autologous ATMPs, as we understood that it means that in case of comparison between autologous products, the outcome will be in favor of similarity, but were wondering what the outcome would be in case of comparison between autologous and allogeneic products.