From: [redacted]
Sent: [redacted]
To: SANTE PHARMACEUTICALS B5
Cc: [redacted]
Subject: Consultation on Concept of 'similar medicinal product' in the context of the orphan legislation: adaptation to technical progress

European Commission
DG Health and Food Safety
Unit B5 "Medicines – policy, authorisation and monitoring"
B-1049 Brussels (Belgium)

Ref: Consultation on Concept of 'similar medicinal product' in the context of the orphan legislation: adaptation to technical progress

Dear Sirs,

Please find below the comments from [redacted].

General comments:

Apart from the adaptation to technical progress of the definition of “similar medicinal product” stated at the Article 3 paragraph (3) of Commission Regulation 871/200, the definitions of the “same therapeutic indication” and “clinically superior” stated at the Regulation (EC) No 141/2000 and Commission Regulation (EC) No 847/2000 should be also reviewed.

Article 8 paragraph 3.c of Regulation (EC) No 141/2000 on orphan medicinal products derogates the general rule of 10 year exclusivity for a granted orphan medicinal product, stating that a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if 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.

Many diseases, including the genetic rare diseases, may vary in each patient and depending on its phenotype multiple different clinical subpopulations might be defined which, in diseases with very low prevalence, the definition of the “same therapeutic indication” not only does not reflect the clinical reality but also impacts the clinical trial design. Thus the ‘same therapeutic indication’ definition might be an additional issue to be addressed to apply Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products.

Additionally, ‘Clinically superior’ is defined in Article 3 paragraph 3.d of Commission Regulation (EC) No 847/2000 as: 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; or (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.

Despite the above definition, a number of genetic rare diseases, in particular the chronic degenerative ones, do not have a validated biomarker and their clinical progression might be very slow and may vary depending on the phenotype. Therefore, the demonstration of clinical superiority may take very long-term studies. Thus it might be worth to also review the definition of "clinically superior".

Specific comment on consultation document Concept of 'similar medicinal product' in the context of the orphan legislation: adaptation to technical progress:

Lines 112-117

Comment:

Different approaches for administration of a similar gene therapy medicinal product, in particular using different routes of administration, can translate in very different bioavailability, biodistribution, safety and efficacy profiles. We propose that the text needs to include a mention that differences in the approach for administration to the patients might significantly affect the biological characteristics and functional impact, including the immune response, and/or the activity relevant to the intended therapeutic effect of the product.

Proposed change: Addition of the highlighted wording.

112 (bb) Two gene therapy medicinal products when there are differences in the therapeutic
113 sequence, viral vector, transfer system, regulatory sequences, or approaches for administration (including administration route) 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.

Please note that the above comments can be directly published provided that my organisation remains anonymous. I declare that nothing within my response is unlawful or would infringe the rights of any third party in a manner that would prevent publication.

Looking forward to hearing from the conclusions and outcome of the consultation,

Best regards,

[redacted]

[redacted]