

Response to the public consultation on the concept of 'similar medicinal product' in the context of the Regulation (EC) No 141/2000 on orphan medicinal products

About the Alliance for Regenerative Medicine:

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 250+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community. Our aim is to connect all parts of the innovation lifecycle to address the unmet needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit <http://www.alliancerm.org>.

This contribution represents the consolidated view of ARM members. The full list of members is provided at the end of this document.

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Comments on the Consultation Document:

On 27 July 2016, the European Commission has launched a public consultation on the concept of 'similar medicinal product' in the context of the orphan legislation. The aim is to improve the implementation of the regulatory framework and to adapt the regulations to technical progress.

For the first time, the consultation document defines the concept of similarity for an Advanced Therapy Medicinal Product (ATMP) in the context of the Regulation (EC) 141/2000 on orphan medicinal products (the 'Orphan Regulation').

The Alliance for Regenerative Medicine (ARM) welcomes this consultation document aiming to clarify certain provisions of the Orphan Regulation and would like to stress that the definitions and provisions in the document should be used exclusively in the context of this Orphan Regulation.

According to the proposed document (lines 99-118), *"An active substance is not considered similar in cases of:*

(aa) ATMPs for which principal molecular structural features cannot be fully defined and the similarity between two active substances needs to be assessed on the basis of biological and functional characteristics. In particular the following considerations apply in order to conclude whether two related cell-based medicinal products are not similar:

- *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.*
- (bb) Two gene therapy medicinal products 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.*
- (cc) Genetically modified cells. The considerations under (aa) and (bb) apply.”*

It is acknowledged that research and development for advanced therapies (ATMPs) is rapidly evolving and that at present, no precedents have been set for similarity assessments of ATMPs. It is also important that any similarity criteria can evolve in parallel with scientific and technical progress. However, regulatory predictability is critical for a developer to be able to decide whether to invest in a development program.

Given that it may be premature to set specific criteria on similarity for ATMPs in the EU legislation, ARM proposes that COMP and CAT release a “Reflection Paper” (similar to the Reflection Paper on ATMP classification for example) or a “Questions & Answers” document to provide further clarity on how the general principles on the structural features, biological and functional characteristics are likely to be applied.

Such Reflection Paper or Questions & Answers could provide examples such as to illustrate:

- when molecular structural features would be considered fully defined for an ATMP?
- when differences in the therapeutic sequence viral vector, transfer system or regulatory sequences have a significant impact on the biological characteristics/activity relevant for the intended effect of gene therapy medicinal products?
- when there are differences in manufacturing technology, what would be considered a significant impact related to the biological characteristics/therapeutic effect?

It would then be helpful if this document could be updated as real examples become available.

In addition, ARM believes the proposed definition is too general, particularly for cell-based medicinal products. The similarity assessment should be multifactorial and should not only be based on the composition and manufacturing technology but should also take into account the principal mode of action and mode of delivery which could influence the efficacy and safety profile of the ATMP. It would therefore be beneficial to explicitly mention the mode of action and mode of delivery as part of the considerations for a multifactorial assessment.

Finally, ARM would like to request more transparency on the justification for similarity/non-similarity assessment for all orphan medicinal products, irrespectively of their nature (ATMPs or not). This would provide greater clarity on the case-by-case evaluation by the EMA and would allow the holder of the marketing authorization of a first product with the same orphan indication to evaluate whether there would be grounds to appeal the decision. It is therefore requested that the EC (or CHMP/CAT) publishes the elements and criteria justifying its decision on the similarity/non-similarity of any orphan medicinal product shortly before or after approval (e.g. as part of the EPAR) or at least inform the marketing authorization holder of a product with the same orphan therapeutic indication of such evaluation.

ARM Members List:

4D Molecular Therapeutics - AABB - Abeona Therapeutics - Accelerated Biosciences - AGTC - Akron Biotechnology, LLC - Aldevron - Alliqua BioMedical - AlloSource - Alpha-1 Foundation - Amaranthus BioScience - American Association for Dental Research - American Association of Tissue Banks - American Society of Plastic Surgeons - Anagenesis Biotechnologies - Andalusian Initiative for Advanced Therapies - Angiocrine Biosciences - AOF Ptc, Ltd - Argos Therapeutics - Asclepius Labs Inc - ASGCT - Asset Management Company - Association of Clinical Research Organizations - Asterias Biotherapeutics - Athersys, Inc. - Audentes Therapeutics - Avalanche Biotechnologies - Avectas - AveXis Therapeutics - Avita Medical - AVROBIO inc - Axiogenesis AG - AxoGen, Inc. - Bamboo Therapeutics - Baxalta (Shire) - Baylor College of Medicine, Center for Cell and Gene Therapy Bellucum Pharmaceuticals, Inc - Benitec BioPharma - BioBridge Global - BioCardia - BioCision - Biogen - BioLife Solutions, Inc.- Biomatrix - Biostage Inc - Blood Centers of America - bluebird bio - Bone Therapeutics - BrainStorm Cell Therapeutics - Brammer Bio - Caladrius Biosciences, Inc. - California Institute for Regenerative Medicine Californians 4 Cures - Calimmune, Inc. - Capricor Therapeutics, Inc. - Celgene Corporation - Cell and Gene Therapy Catapult - Cell Medica - Cell Therapies Ltd. - Cellect Bio - Cellectis - CellGenix GmbH - Cellixir - CellProthera - Cellular Dynamics International, a Fujifilm Company Cellular Technology Limited - Celsense Inc. - Celyad - Centre for Commercialization of Regenerative Medicine Cesca Therapeutics - Chemelot Campus B.V. - Cleveland Clinic - Cleveland Cord Blood Center - Coalition for Clinical Trials Awareness - Cognate BioServices - CombiGene AB - Commence - Bio (Wibi+Works Therapeutics) - Cord Blood Registry (AMAG Pharmaceuticals) - Cornell University - CRC for Cell Therapy Manufacturing - Cryoport Systems - CTI Clinical Trial and Consulting Services - CWRU-NCRM - Cyfuse Biomedical - Cynata Therapeutics Inc. - CytoVac - Dimension Therapeutics - DiscGenics, Inc. - Dohmen Life Science Services - Editas Medicine - Embody LLC - EMD Serono - Emendo Bio - ESGCT - EveryLife Foundation for Rare Diseases - Evidera - Fate Therapeutics - Fibrocell Science - Fight Colorectal Cancer Research Center - Fondazione Telethon (San Raffaele-Telethon Institute for Gene Therapy) Foundation for Biomedical Research and Innovation - Fraunhofer Institute for Cell Therapy and Immunology - Fred Hutchison Cancer Research Center - Frequency Therapeutics - GE Healthcare -Gemstone Biotherapeutics LLC - GenSight Biologics - GenVec - GlaxoSmithKline - Global BioTherapeutics - Global Genes - GreenCross LabCell - Gri-Cel, S.A.- Haack & Associates - Healios K.K. - HemoGenix, Inc - Hemostemix - Histogenics - Holostem - Human Organ Project, Inc. - Huntington Medical Research Institutes - Immusoft - Institut Clayton de la Recherche - Intellia Therapeutics - International Society for Stem Cell Research - Invetech - InVivo Therapeutics - Irvine Scientific - jCyte - JETRO NY - Johns Hopkins University - Johnson & Johnson (Janssen R&D) - Juno Therapeutics - Juventas Therapeutics - Kawasaki Heavy Industries - KeyBiologics - Kiadis Pharma - Kite Pharma - Lake Street Capital Markets - LogicBio - Longeveron - Lonza Group Ltd. - Lysogene - MaSTherCell - MaxCyte, Inc. - Medipost America - Medpace - Memorial Sloan-Kettering Cancer Center - Mesoblast Limited - Michael J. 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