EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Updated EC Q&A on similarity for ATMPs in the context of the Orphan legislation

Version 2, April 2021

6th Industry Stakeholder Platform on R&D support – 4th June 2021

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Regulatory framework

- Regulation (EC) No 141/2000 (Article 8(1)) on orphan medicinal products adopted to promote the research, development and marketing of medicinal products for rare diseases. Article 8(1) of Regulation (EC) No 141/2000 states that

  *"…the Community and the Member States shall not, for a period of **10 years**, accept another application for a marketing authorisation (MA), or **grant a MA** or accept an application to **extend an existing MA**, for the same therapeutic indication, in respect of a **similar medicinal product**." (emphasis added)*

  - Assessment of similarity (module 1.7.1) required in case of authorised OMPs.
  - For ATMPs - assessed by CAT and final opinion adopted by CHMP.

CAT: Committee for Advanced Therapies
CHMP: Committee for Medicinal Products for Human Use
ATMP: Advanced Therapy Medicinal Product

Regulatory framework (cont'ed)

- Definition of "**similar active substance**" in REG (EC) No 847/2000 modified in 2018 (COM Regulation 2018/781) for biological products and ATMPs
  - 'Similar medicinal product' = medicinal product containing similar active substance(s) and which is intended for the same therapeutic indication.
  - 'Similar AS' = AS with the same principal molecular structural features and which acts via the same mechanism, **however for ATMPs**
  - **similarity is assessed based on biological and functional characteristics** relevant for the intended therapeutic effect and/or safety attributes of the product.

E.g., cell-based ATMPs: ***differences in starting materials, the final composition or manufacturing technology*** *with a* ***significant*** *impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.*

Similarity vs. New Active Substance (NAS)

Similarity	New Active substance
Triggered by any authorised OMP with market exclusivity.	Triggered by claim / comparison with any MP for any indication subject to a MA in the EEA.
Concept broader than NAS : ➲ Known/same active substances are always similar. ➲ New active substances (NAS) can be either non similar or similar.	**Not previously authorised** in a medicinal product for human use in the EU, OR **differing significantly in properties with regard to safety and/or efficacy.**
Impacts **approvability of the product.**	Amongst else, linked to **data protection** (start of Global Marketing Authorisation).

Note: Draft Guidance on the structure and properties for the determination of NAS status of biological substances ***UNDER DEVELOPMENT***

EC Q&A related to the assessment of similarity

- Version 1– 25 May 2018

1. Does the **route of administration** play a role in the assessment of similarity?
2. In the case of ATMPs, **differences in the manufacturing technology** can be relevant to demonstrate non-similarity between two products. What is the meaning of "manufacturing technology"?
3. Which **safety attributes** are relevant for the purposes of assessing similarity between two ATMPs (e.g., ablation mechanism)
4. Are all **differences in the therapeutic gene sequence, viral vector, transfer system, or regulatory sequences** relevant for the purposes of assessing similarity between two gene therapy medicinal products?

Note: Strength and pharmaceutical form not relevant for assessment of similarity.

EC Q&A related to the assessment of similarity

Version 2 – April 2021

- Updated to reflect latest experience and clarify expectations on level of evidence
- Additional Questions
  - 5. What **differences in the starting materials** may be considered relevant to support a claim of non-similarity?
  - 6. Can a **difference in principal molecular structural features** be considered relevant to support a claim of non-similarity?
  - 7. **What level of evidence should be provided** to demonstrate that differences in the biological characteristics and/or biological activity are relevant for the intended therapeutic effect and/or safety attributes of the product?

https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/2018_qa_atmps_en.pdf

Key update – examples of non-similarity claims

- [Q2] For a cell-based product - **improved consistency of the composition of the active cell population** of relevance for the R/B (e.g., difference in selection procedure (manufacturing technology)).
- [Q2] Difference in the manufacturing process **expanding the treatable population (within the same indication)**, such as patients with lower initial starting material target cell counts (manufacturing technology).
- [Q3] Introduction of an **ablation mechanism** to address potential toxicities or **reduction in risks** (e.g., immune responses, insertional mutagenesis) (safety characteristics).

Key update - examples of non-similarity claims

- **[Q4] Gene Therapy :** 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.
  - E.g., for **viral vectors (in vivo), differences in virus capsid** that reduce immune response or permits expanding the treatable population OR changes that reduce the risk of insertional mutagenesis.
- Q5 - Differences in **starting materials**, e.g., use of **primary cells** vs. a **cell line** OR **use of tumor** vs. **non-tumour** cell lines.

Key update – level of evidence expected (Q7)

- **Clinical data not required**. Justification based on **plausible scientific grounds** e.g. based on scientific literature or available in-vitro data/ in-vivo (non-)clinical data. Clinical data may be used, *if available.*
- Applicants to rely on **information that is publicly available** or that is otherwise accessible.
- Assessment of similarity between two ASs does not entail demonstration that the new product is safer, more effective or otherwise superior clinically.
- For ATMPs, applicants are **not required to demonstrate non-similarity against all of the parameters** referred in Section (3) of Article 3(3) of Regulation (EC) No 847/2000.

Thanks to Rocio Salvador Roldan (EC), CAT members and EMA colleagues.

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- Reviewers: EMA (Quality/Legal/RA/Orphan); BWP; CAT.

BWP: Biologics Working Party
RA: Regulatory Affairs Office

Thank you for your attention

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