



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper for the development of a Reflection Paper on a tailored clinical approach in Biosimilar development

Agreed by Biosimilar Medicines Working Party	29 November 2023
Adopted by CHMP for release for consultation	25 January 2024
Start of public consultation	01 February 2024
End of consultation (deadline for comments)	30 April 2024

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Keywords	Reflection Paper, Biosimilar, Comparative Efficacy Study, Tailored clinical approach
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1. Introduction

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (Reference Medicinal Product, RMP), where similarity to the reference medicinal product based on a comprehensive comparability exercise has been established. Biosimilars have become important therapeutic options, improving patient access to essential treatments. Therefore, CHMP (EMA) acknowledges the significance of biosimilars.

Currently, the required comparability exercise comprised quality data (analytical comparability exercise), in vitro and in vivo non-clinical data, and comparative pharmacokinetic, pharmacodynamic, safety and efficacy studies. However, considering the advances in the analytical sciences and the extensive regulatory experience gained, in vivo non-clinical data and, at least for some less complex biologicals with a straightforward mechanism of action, the importance of dedicated clinical efficacy and safety data should be re-evaluated. Currently, the need for Comparative Efficacy Studies (CES) is increasingly questioned in general.

2. Problem statement

Biosimilar medicines cover a broad array of products, ranging from relatively simple to more complex molecules. The CHMP has accumulated substantial experience in assessing biosimilars with high complexity such as monoclonal antibodies (mAbs), resulting in a robust regulatory framework that ensures product efficacy and patient safety. An ever-growing number of biosimilars has been successfully authorized through rigorous evaluation of scientific data, including the assessment of comparability for quality, non-clinical, and clinical aspects. By building upon this extensive knowledge, CHMP aims to further optimize the development and evaluation process for biosimilars.

Constantly striving for scientifically sound yet efficient processes, the Biosimilar regulatory framework has constantly been evolving towards increasingly tailored developments, starting from smaller and “simpler” biologics, such as recombinant Granulocyte-Colony Stimulating Factor (rG-CSF), insulins or somatropin where the need for comparative clinical efficacy trials is in general not required any more. With growing knowledge and the increasing possibilities of analytical and functional characterisation, revisiting the need for clinical efficacy trials for biosimilars (especially recombinant proteins and mAbs) is considered the next important step in order to keep the Biosimilar pathway attractive for developers and, at the same time, guarantee future access to safe and efficacious biologics for European patients.

3. Discussion (on the problem statement)

CHMP has gained extensive insight into assessing the quality attributes of biosimilars through the evaluation of critical quality attributes, manufacturing processes, and comparability exercises. The Agency has closely examined physicochemical and functional characteristics, as well as the overall similarity to the RMP. This experience has led to the establishment of stringent requirements and guidance that ensure the quality of biosimilars, including biosimilar mAbs. The CHMP recognizes that there may be the potential to waive certain clinical data requirements even for complex biosimilars such as mAbs based on solid evidence of quality comparability. When the biosimilar demonstrates a high degree of similarity to the RMP at the analytical and functional level, it may be possible to justify the omission of dedicated CES.

This approach aims to streamline the development and evaluation process while maintaining the highest standards of safety and efficacy. Whether and which clinical data will be required may depend on how well the clinical performance of the biosimilar can be predicted from comparative experiments on the analytical/functional level, knowledge regarding the molecule’s mode of action (primary and secondary pharmacology) and also the clinical profile of the RMP, e.g. the potential and impact of immunogenicity.

The aim of the proposed reflection paper will be to discuss CHMP's perspective on the development and evaluation of biosimilars, taking into account the wealth of experience gained from previous marketing authorizations, particularly in relation to analytical/functional comparability exercises. More accurately, the reflection paper will explore how far well-defined analytical/functional (quality) data can be predictive for the clinical outcome.

In consequence, it will be evaluated, whether, or not, findings from a quality comparability exercise, together with clinical PK/PD trials could prospectively lead to the conclusion of clinical similarity, without the need for large CES in patients.

4. Recommendation

In response to the evolving landscape of biosimilars in general and the increasing requirement for scientifically sound yet efficient regulatory processes, CHMP acknowledges the possibility for further tailoring of the clinical approach for biosimilars and emphasizes the wealth of experience gained from previous marketing authorizations, particularly in quality comparability. A reflection paper is considered valuable to guide both developers and assessors of biosimilar medicinal products.

5. Proposed timetable

The concept paper will be released for consultation for a three month public consultation period.

BMWP will take account of all comments received during the public consultation on the concept paper when preparing the draft guideline. The draft Reflection Paper will be published for a six-month public consultation period.

BMWP will take account of all comments received during the public consultation on the draft Reflection Paper when preparing the final text. It is expected that the final Reflection Paper will come into operation three months after publication following adoption by CHMP.

6. Resource requirements for preparation

The development of the Reflection Paper will involve the EMA-BMWP Secretariat, the Biosimilar Medicines Working Party, the Biologics Working Party, the Methodology Working Party and Scientific Advice Working Party, who would be consulted, as necessary.

The BMWP will appoint a rapporteur and drafting group.

7. Impact assessment (anticipated)

The Reflection Paper will outline current thinking on the need for CES with a view to improving the efficiency of biosimilars development.

The implementation of the proposed recommendations would reduce the need for human studies in the comparison of a biosimilar medicine under development to the RMP.

8. Interested parties

Academia, Pharmaceutical Industry, EU Competent Authorities and patients and health care professional groups.

9. References to literature, guidelines, etc.

Relevant EU and International guidelines on biosimilars development.

Overarching biosimilar guidelines

Guideline on similar biological medicinal products, CHMP/437/04 Rev 1, 23 October 2014

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), EMA/CHMP/BWP/247713/2012, 22 May 2014

Product-specific biosimilar guidelines

Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues), EMEA/CHMP/BMWP/31329/2005, London, 22 February 2006

Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins, EMEA/CHMP/BMWP/118264/2007 Rev. 1, 10 November 2016

Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues, EMEA/CHMP/BMWP/32775/2005_Rev. 1, 26 February 2015

Guideline on similar biological medicinal products containing interferon beta, EMA/CHMP/BMWP/652000/2010, 21 February 2013

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, EMA/CHMP/BMWP/403543/2010, 30 May 2012

Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins, EMEA/CHMP/BMWP/301636/2008 Rev. 1, 28 June 2018

Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH), EMA/CHMP/BMWP/671292/2010, 21 February 2013

Guideline on similar medicinal products containing somatropin (Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues), EMEA/CHMP/BMWP/94528/2005 Rev. 1, 28 June 2018

Other guidelines relevant for biosimilars

Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues, EMEA/CHMP/BMWP/101695/2006, 19 July 2007

IGuideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, EMEA/CHMP/BMWP/14327/2006 Rev 1, 18 May 2017

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use, EMA/CHMP/BMWP/86289/2010, 24 May 2012

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