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2 EMA/CHMP/BMWP/35061/2024
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper for the development of a Reflection Paper**
5 **on a tailored clinical approach in Biosimilar development**
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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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10 **1. Introduction**

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

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

23 **2. Problem statement**

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

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

39 **3. Discussion (on the problem statement)**

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

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

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

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

61 **4. Recommendation**

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

67 **5. Proposed timetable**

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

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

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

75 **6. Resource requirements for preparation**

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

79 The BMWP will appoint a rapporteur and drafting group.

80 **7. Impact assessment (anticipated)**

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

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

85 **8. Interested parties**

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

88 **9. References to literature, guidelines, etc.**

89 Relevant EU and International guidelines on biosimilars development.

90 **Overarching biosimilar guidelines**

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

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

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

96 **Product-specific biosimilar guidelines**

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

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

102 Guideline on non-clinical and clinical development of similar biological medicinal products containing
103 recombinant human insulin and insulin analogues, EMEA/CHMP/BMWP/32775/2005_Rev. 1, 26 February
104 2015

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

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

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

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

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

117 **Other guidelines relevant for biosimilars**

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

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

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

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125 Relevant Literature References

- 126 Guillen, E., Ekman, N., Barry, S., Weise, M. and Wolff-Holz, E. (2023), A Data Driven Approach to Support
127 Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. *Clin Pharmacol Ther*, 113: 108-123.
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- 129 Kirsch-Stefan, N., Guillen, E., Ekman, N. et al. Do the Outcomes of Clinical Efficacy Trials Matter in
130 Regulatory Decision-Making for Biosimilars?. *BioDrugs* 37, 855–871 (2023).
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