# Submission of comments on the draft "Reflection paper on a tailored clinical approach in biosimilar development"

Fields marked with * are mandatory.

## Introduction to the survey on the draft Reflection paper on a tailored clinical approach in biosimilar development

Please click here to be redirected to the guideline text. The public consultation is launched on 1 April 2025 until 30 September 2025.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section.
**If you need more rows to be added to the table, please contact dora.duarte@ema.europa.eu**
Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 September 2025) by clicking on "Edit contribution" in the link https://ec.europa.eu /eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

## Data Protection Statement

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

**EMA Privacy Statement**

All personal data provided within this survey will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union Institutions and bodies on the free movement of such data.
For more details on how EMA processes personal data, please refer to the EMA Data Protection Notice for surveys conducted via EUSurvey: https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-data-protection-notice-conducting-surveys-eusurvey_en.pdf
If you have any questions, complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu
You can contact the Internal Controller at datacontroller.humanmedicines@ema.europa.eu
You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu

* Please confirm that you have read and understood the data protection notice and you consent to the processing of your personal data.
  - (●) Yes

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.
  - (●) Yes
  - ( ) No

Should you not want to give consent to publish, please send your objections to datacontroller.humanmedicines@ema.europa.eu

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

For additional information, please consult EMA's privacy statement.

## Your details

* Name of organisation or individual

European Federation of Pharmaceutical Industries and Associations

* Country of organisation or individual

Belgium

* Email

par.tellner@efpia.eu

If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

## 1. General comments

## 1. General comments

| | General comment |
|---|---|
| 1 | EFPIA is pleased to provide its comments to the EMA regarding the draft “Reflection paper on a tailored clinical approach in biosimilar development”. These comments were developed with the joint support from the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA). EFPIA recognises the crucial role of biosimilars in the healthcare system, expanding patient access to treatments. We fully support their development and access, not only in the EU but also in emerging markets. |
| 2 | We acknowledge the evolution of regulatory science since the introduction of the first biosimilars. Evidence accumulated over the years suggests that Comparative Efficacy Studies (CES) may not always be required. However, it is important to note that this approach is not applicable to all products and that, therefore a case-by-case evaluation remains essential. This is supported by Guillen et al. (2025) in their article incl. a discussion on patient safety and immunogenicity considerations (https://doi.org/10.1007/s40265-025-02168-y, page 606). |
| 3 | Maintaining rigorous regulatory standards is essential to ensure biosimilar quality, safety, and efficacy. We are committed to collaborating with healthcare authorities, professionals, and patient organizations to ensure that biosimilar introduction does not compromise therapeutic outcomes. |
| 4 | We value EMA's careful approach, from the 2024 concept paper to the current reflection paper, and appreciate that our comments have been thoroughly considered in this continuous dialogue. |
| 5 | EFPIA welcomes the key points incorporated in the reflection paper, notably: · Maintaining high scientific standards while considering a tailored approach. · Prerequisites for analytical similarity assessment. · The continued importance of immunogenicity assessment. · Recognition that certain complex biologicals may require comparative efficacy studies. |
| 6 | EFPIA suggested overall improvements: · Product and process-impurities including stability indicating parameters and impurity profile should also be discussed. · Pre-requisites should be more clearly explained to justify the waiver of CES, since the tailored approach is not simply quality related. · The statistical section could be further clarified and harmonised, contributing to identify and address differences between the reference product and the biosimilar candidate. |

| | |
|---|---|
| 7 | EFPIA also is of the view that comparative pharmacokinetic and pharmacodynamic (PK/PD) studies in small sample size may not always be sufficient for biosimilar programs to assess similarity in safety and immunogenicity across the broader intended use patient population. While these studies can provide valuable information on the dose and effect relationship, they might not capture long-term safety concerns or the full immunogenic profile of biosimilars as compared to the reference product. It is therefore essential to consider when additional methods beyond PK/PD studies are appropriate to thoroughly evaluate the comparative safety and immunogenicity of these products. |
| 8 | In addition, EFPIA would also suggest the inclusion of a dedicated section within the reflection document regarding pharmacovigilance practices for biosimilars, which are crucial to ensure comprehensive oversight and enhance the monitoring of all biologics, including biosimilars', safety and efficacy. In addition, EFPIA would also suggest the inclusion of a dedicated section within the reflection document regarding pharmacovigilance practices for biosimilars, which are crucial to ensure comprehensive oversight and enhance the monitoring of all biologics, including biosimilars', safety and efficacy. |
| 9 | While existing experience with monoclonal antibodies could support a tailored approach for these molecules when well-characterised, maintaining an integrated approach based on the totality of evidence remains crucial as a general principle. Furthermore, vaccines, ADCs as well as advanced therapy medicinal products (ATMPs) may be explicitly excluded from a tailored approach. |
| 10 | EFPIA proposes the inclusion of a decision tree diagram to help address cases where a CES would still be required. Such a decision tree with examples could provide a structured framework for making informed decisions regarding the need for CES, especially when residual uncertainties exist. Such a diagram could clarify and simplify complex choices, provide transparency and predictability to manufacturers, and ensure that critical factors are considered. |
| 11 | 11. EFPIA is dedicated to working with EMA to ensure safe and effective biosimilar development while streamlining the regulatory approval process for the benefit of patients, healthcare systems, and sponsors. Please find detailed comments provided in the subsequent sections of our response. |
| 12 | |
| 13 | |
| 14 | |
| 15 | |
| 16 | |

| | |
|---|---|
| 17 | |
| 18 | |
| 19 | |
| 20 | |
| 21 | |
| 22 | |
| 23 | |
| 24 | |
| 25 | |
| 26 | |
| 27 | |
| 28 | |
| 29 | |
| 30 | |

# 2. Specific comments

## 2.1. Introduction

## 2.1. Introduction

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 53-57 | Industry accepts that advances in technology and understanding have enabled most changes to be made to reference product manufacturing without clinical studies (reference to be added by EMA if available). However, a major difference for a biosimilar is the absence of product and process knowledge compared to the originator MAH. As such, a reference to manufacturing changes as made is not necessarily valid in a biosimilar context. There is a significant difference between mitigating risks associated with changing an existing process and introducing a new biosimilar product and process. When assessing a change, the MAH of the reference product has access to development and lifecycle data that cannot be used for a biosimilar (e.g., whether the cell line or the mother cell bank is the same pre- and post-change, which elements of the process have been changed). The MAH of the reference product often has access to samples and intermediates in the process to support comparability as well as long term stability trends for DS and DP attributes that the sponsor of a proposed biosimilar does not. As per ICH Q5E, the extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others: quality comparability, nature and level of knowledge of the product, existing nonclinical and clinical data relevant to the product, aspects of product use and product class, including immunogenicity /safety risks. As such, it is not appropriate to compare the scientific approach MAHs can apply per ICHQ5E to originator products with the situation of initial approval of | GENERAL: Quotation marks is used to indicate words or text which should be deleted. CAPITAL LETTERS are used to indicate words or texts, which should be added. Suggest modifying or add supportive publication /reference. The following text should be deleted (indicated with quotation marks.) "This scientific principle has been widely accepted and used to support changes in the manufacturing processes of biological products with well-defined structural attributes. Significant changes in the manufacturing processes of biological medicines like monoclonal antibodies have been approved by confirmation of structural and functional comparability through a comprehensive comparative analytical testing without the need for new clinical data." This "experience" PRINCIPLE , together with technical advances in analytical characterisation, supports the notion that under specific prerequisites, analytical comparability exercises and pharmacokinetic (PK) data could be sufficient for demonstrating biosimilarity. |

| | | | |
|---|---|---|---|
| | | biosimilars and the sentence “analytical comparability exercises and pharmacokinetic (PK) data could be sufficient for demonstrating comparability” should also be revised. | |
| 2 | 69-72 | It is acknowledged that a CES may be difficult to conduct, especially in rare diseases, and that unnecessary clinical studies are unethical and should be avoided. However, appropriate innovative study designs may be contemplated to overcome challenges to conduct a CES. Finally, the fact that a CES may be difficult to conduct is not a legitimate reason to waive a CES if considered necessary for scientific reasons. | Propose deleting the paragraph. |
| 3 | 73-76 | It is proposed to better address the aspect that all levels of comparability are to be considered. | Taken together, a regulatory option that, under certain prerequisites, allows authorisation based on demonstrated COMPREHENSIVE comparability (INCLUDING QUALITY ASPECT) "at the quality level" with a limited... |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |

| | | | |
|---|---|---|---|
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

## 2.2. Scope

### 2.2 Scope

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

## 2.3. Discussion

### 2.3.1. Quality

### 2.3.1.1 General basis and background

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 110 | “The concept of comparability allows to take into consideration quality differences….” We recommend rephrasing this text for additional clarity. | The concept of comparability allows FOR CERTAIN to take into consideration quality differences…. |
| 2 | 115-117 | The comparability exercise is not restricted to physicochemical characteristics. ICH Q5E stipulates: “A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data.”, “the need for stability data…” as well as immunochemical properties (if applicable), purity, impurities and contaminants should be considered. The reflection paper seems to restrict the comparability to physicochemical aspects, whereas the analytical comparability incorporates also biological activities, immunochemical properties, stability and impurity profile. | Since the 1990s, major manufacturing changes have been substantiated and implemented based on comparability exercise, COMPRISING OF A VARIETY OF TECHNIQUES SUCH AS ANALYTICAL, BIOLOGICAL, AND STABILITY TESTING and without… |
| 3 | 115-118 | This sentence may need to be further supported by (public) evidence from holistic review of post approval changes or nuanced (see also comment to lines 53-57). As per ICH Q5E, a risk-based approach should be considered with supportive nonclinical and/or clinical data to establish comparability pre and post-changes. A major difference for a biosimilar is the absence of prior knowledge compared to the originator and the overall synergistic impact of multiple changes including changes to the manufacturing process, which, by essence, is different from the manufacturing process used for the RMP. As per ICH Q5E, the extent and nature of nonclinical and clinical studies will be determined on a | Please add references or remove lines 117-118: This includes situations … biosimilar product. |

| | | | |
|---|---|---|---|
| | | case-by-case basis in consideration of various factors, which include among others: quality comparability, nature and level of knowledge of the product, existing nonclinical and clinical data relevant to the product, aspects of product use and product class, including immunogenicity/safety risks. | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.2 Prerequisites for similarity assessment

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 137-139 | It is not sufficiently clear what is meant by “relevant” QAs. The comprehensive set of relevant QAs should not be restricted to structural and functional properties, but should also include purity, impurities and contaminants, as well as stability (for example, a contamination of the drug product with a process-related protease may compromise the stability of the product), even if not formally part of the similarity assessment (SAP). | A comprehensive set of QAs (INCLUDING STABILITY INDICATING PARAMETERS) providing detailed information regarding the structural and functional properties of the biological molecule, AS WELL AS ITS POTENTIAL IMPURITIES is essential for the demonstration of similarity between a biosimilar candidate and its RMP. |
| 2 | 142-149 | In line with the previous comment, the assessment of criticality of QAs should not be restricted to QAs impacting the interaction with receptor but include as well impurities and contaminants that can be highlighted as stability indicating CQAs (e.g. protease, lipase…). | Prior knowledge provides understanding of the critical QAs (CQAs) impacting the interaction with receptor(s) (including membrane receptors, ligands, substrates, and other targets), IMPURITIES THAT CAN BE HIGHLIGHTED AS STABILITY-INDICATING CQAS ETC. These ATTRIBUTES MAY HAVE biological effects... |
| 3 | 166-167 | The purity, impurities, contaminants and stability indicating parameters are missing from the list of pre-requisites as per Guideline on similar biological medicinal products containing biotechnology-derived protiens as active substance https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance-quality-issues-revision-1_en.pdf | Line 166-167: - detailed characterisation of CQAs impacting structure function relationship as well as PRODUCT PURITY, IMPURITIES, "product variants", CONTAMINANTS AND STABILITY INDICATING PARAMETERS is possible using orthogonal and state-of-the-art analytical methods; |
| | | | We suggest replacing lines 165-173 with the following criteria to be considered for a risk-based approach to conduct a CES: 1 The complexity of the reference |

| | | | |
|---|---|---|---|
| 4 | 165-173 | CES remain required for biosimilar development, unless specific conditions are met. We therefore suggest considering as pre-requisites a priori risk-based criteria (not only quality also context of use) to plan a CES as part of the SAP or to justify why a tailored clinical development approach is considered applicable or not in this section, based on the following literature*. *Bielsky, M.-C., Cook, A., Wallington, A., Exley, A., Kauser, S., Hay, J. L. et al. (2020). Streamlined approval of biosimilars: Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial - PubMed (nih.gov) https://pubmed.ncbi.nlm.nih.gov/32916269/ WHO. Guideline on the evaluation of biosimilars. Available from: WHO Guidelines on SBPs Stebbing, J., Mainwaring, P. N., Curigliano, G., Pegram, M., Latymer, M., Bair, A. H., & Rugo, H. S. (2020). Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 38(10), 1070–1080. Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars - PubMed https://pubmed.ncbi.nlm.nih.gov/32058846/ Wolff-Holz, E., Tiitso, K., Vleminckx, C. et al. (2019). Evolution of the EU Biosimilar Framework: Past and Future. BioDrugs 33, 621–634. Evolution of the EU Biosimilar Framework: Past and Future - PMC https://pmc.ncbi.nlm.nih.gov/articles/PMC6875146/ Guillen E., Barry S. , Jost N., et al. (2025). The Tailored Biosimilar Approach: Expectations and Requirements. Drugs (2025) 85:601–608https://doi.org/10.1007/s40265-025-02168-y | product · larger molecular size, active ingredient difficult to isolate · diverse moieties with different functions, complex mixtures · multiple mechanisms of action · potential for immunogenicity and potentially life-threatening adverse effects (ADA incidence and/or the magnitude of ADA response including level of neutralizing antibodies, and antibodies targeting endogenous substances, correlating with clinical sequelae) 2 The knowledge of the RP · Sufficient batches of RP can be analysed to reflect the variability of the RP over its shelf life · Analytical methods are sensitive, qualified and sufficiently discriminatory, with orthogonal methods used wherever possible · Range of variability is defined at analytical and in vitro functional levels · Functional assays are relevant for the MoAs in all indications 3 The magnitude of differences expected in comparative structural and functional assessments makes it difficult to predict the impact 4 The degree to which the mechanism of action(s) is understood in different indications and how well these can be investigated in binding and functional in vitro tests ; Well known structure function relationship for every component 5 The level of differences introduced in the biosimilar compared to RP that could give rise to potential clinical/safety and immunogenicity concerns (change of manufacturing process impacting the impurity profile (amount and diversity), and/or change of the nature of excipients and/or change of device affecting the performance and patient experience) 6 The availability of a PD endpoint that correlates with efficacy might be an additional plus 7 Context of use: Clinical setting (e.g, scarcity of population to be studied (rare disease), indication (impact PK/disease relation knowledge), clinical practice (monotherapy vs |

| | | | |
|---|---|---|---|
| | | | combination treatment where CES would be valuable to mimic routine treatment protocols), situations where PK are not relevant (e.g, locally administered products)), use in special patient populations such as pregnant or lactating individuals. |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |

| | | | |
|---|---|---|---|
| 29 | | | |
| 30 | | | |

### 2.3.1.3 Similarity assessment protocol

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.4 Batched to be included in the similarity assessment

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.5 Analytical considerations

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 229-234 | In order to ensure that analytical comparability is the cornerstone of the similarity assessment including for assessing differences impacting quality, efficacy and safety, a robust head-to-head comparison is recommended to be maintained to avoid bias (operator, equipment…) or otherwise exceptions to be justified based on literature with specific examples, in accordance with current Guideline on similar biological medicinal products containing biotechnology-derived protiens as active substance (sections 5.2 and 5.3). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance-quality-issues-revision-1_en.pdf Even if the characterization methods cannot be fully validated, in many cases, they can be qualified to determine the precision of the method and do not prevent side-by side comparison. This will allow to remain consistent and harmonized with other international guidelines and expectations (e.g WHO guidelines on biosimilars). | Replace the following text starting end of line 229 “The previously applied requirements to perform side-by-side analysis have largely become obsolete because most state-of-the-art methods have good analytical precision with little between run/day-to day variability (or, at least, this variability is similar to within day variability /precision). However, side by-side analysis might remain meaningful in a situation with strong between run variability, for example, Surface Plasmon Resonance analysis.” by: ANALYSIS SHOULD INCLUDE SIDE-BY-SIDE COMPARATIVE STUDIES UNLESS OTHERWISE JUSTIFIED. ANY DIFFERENCES DETECTED IN THE IN THE QUALITY ATTRIBUTES WILL HAVE TO BE APPROPRIATELY JUSTIFIED WITH REGARD TO THEIR POTENTIAL IMPACT ON SAFETY AND EFFICACY (SEE GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE SECTION 5.2 AND 5.3). |
| 2 | 235-242 | Considerations related to SAR (Structure-Activity relationship) and functional assays expectations are of major importance. Hence, we propose to clarify that a clear correlation between each CQA and associated potential clinical impact including their description and justification in the similarity assessment protocol will be required. As the MoA can vary significantly depending on the experimental model employed, we propose EMA clarifies that each functional assay should be fully | |

| | | | |
|---|---|---|---|
| | | representative of each MoA within a relevant pathophysiological model, for the actual indication(s) foreseen. Please consider adding an additional chapter or further details related to expectations on functional assays. | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.6 Assessment of physicochemical and functional similarity

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 252-265 | In addition to release testing, considerations related to impurity profiles and stability have an impact on efficacy and safety and need to be considered as part of the totality of evidence, in accordance with the cited guideline EMA/CHMP/BWP/247713/2012 which includes the physicochemical properties, biological activity, immunochemical properties, purity and impurities, quantity, and stability. Differences in impurities—particularly process-related impurities such as host cell proteins or residual DNA—may impact product safety, immunogenicity, and overall clinical performance. | Line 260-262: “The manufacturing control system, including batch release AND STABILITY TESTING for the most critical QAs (PHYSICO-CHEMICAL PROPERTIES, BIOLOGICAL ACTIVITY, IMMMUNOOCHEMICAL PROPERTIES, QUANTITY /POTENCY, IMPURITIES...), ensures that the quality profile of future biosimilar batches remains similar to the batches tested for similarity, as well as to the RMP. Any biosimilar batches "released" within the batch-to-batch variability of the RMP are expected to have the same clinical performance, and differences within the ranges are assumed not to have a relevant impact on safety or efficacy.” |
| 2 | 275-282 | In anticipation of the new ICH guideline Framework for Determining Utility of Comparative Efficacy Studies in Biosimilar Development Programs, we would recommend to harmonize and align with other guidelines /recommendations (e.g. Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry \| FDA, https://www.fda.gov/regulatory-information/search-fda-guidance-documents /development-therapeutic-protein-biosimilars-comparative-analytical-assessment-and-other-quality, WHO biosimilars guideline) to ensure “how far dissimilarity in QA data (or residual uncertainties) can be seen compliant with a biosimilarity claim” taking the entire biosimilar data package as a whole (including in context of a tailored development approach). | |

| | | | |
|---|---|---|---|
| 3 | 283-285 | Please provide a reference for the “population-in-population” approach or clarify how this relates to the approaches described in the reflection paper on statistical methodology (EMA/CHMP/138502/2017). | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| | | | |

| | | | |
|---|---|---|---|
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.7 Uncertainties in the similarity assessment

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 310-364 | Clarity around residual uncertainties should be provided, and what would be acceptable differences in contrast to substantial differences to avoid assessor dependent assessment. It is unclear under which circumstances CES would be needed. It seems it would be seen as last resort as alternative in case the manufacturing process could not be adapted and there would remain residual uncertainties which cannot be justified by functional assays and PK/(PD). Inflating the number of batches of biosimilars and RMPs will in the end not streamline development nor will it rescue or explain differences that may impact quality, efficacy and safety. We recommend therefore to define a risk-based approach that considers a case-by-case assessment of the need for comparative clinical studies a priori with risk-based criteria that could be reflected as pre-requisites in section 3.1.2. In addition to pre-requisites as defined in section 3.1.2, we would suggest a more systematic outline of what is expected when performing the similarity assessment to remove residual uncertainties following a decision tree that could be put in an Annex together with examples. | Consider rewording lines 324-329: "If the similarity criteria are not met for some QAs, and the supporting data package and justifications are insufficient to rule out a possible impact on efficacy or safety, developers should consider adapting the manufacturing process of the biosimilar to better align with the quality profile of the reference medicinal product." IF ANALYTICAL SIMILARITY IS NOT SUFFICIENT TO ENSURE THE ABSENCE OF CLINICALLY MEANINGFUL DIFFERENCES, THEN CES MAY BE REQUIRED. ESPECIALLY, IF THE SIMILARITY CRITERIA ARE NOT MET FOR CERTAIN CQA AND A POSSIBLE IMPACT ON SAFETY OR EFFICACY CANNOT BE RULED OUT, THEN EITHER THE PROCESS NEEDS TO BE ADAPTED TO MEET THE PREDEFINED SIMILARITY CRITERIA OR FURTHER CLINICAL EVALUATION IS NEEDED. IF THE CONTROL STRATEGY IS INSUFFICIENT TO DETECT, IDDENTIFY AND QUANTIFY SUCH DIFFERENCES, FURTHER CINICAL EVALUATION IS ALSO REQUIRED Consider adding a decision tree and examples in Annex. |
| 2 | 349-354 | We recommend making clear that this should apply where the assay’s measure the same activity/point in biological pathway: | Proposed rewording: It is also important to recognise that differences detected using a sensitive assay typically cannot be overcome by providing supportive data from a less sensitive assay WHERE SUCH ASSAYS MEASURE THE SAME BIOLOGICAL ACTIVITY (I.E. BINDING OR SIGNALLING) |
| | | | |

| | | | |
|---|---|---|---|
| 3 | 378-380 | Because difference in binding do not necessarily translate to differences in activity, we recommend some rewording. | Proposed rewording: For example, for mAbs, additional computational modelling showing that the deamidation, oxidation and isomerisation sites are not located in an epitope binding region or Fc region or that any differences observed have no impact on binding AND /OR ACTIVITY may be relevant. |
| 4 | 400-403 | It might be unrealistic to allow for differences in bioassay in the absence of any clinical and safety impact assessment as measurements of bioactivity do not equal pharmacodynamic effects in patients. Orthogonal methods like SPR cannot justify the failure of a bioassay because they look at different aspects of the recognition of a ligand to a specific target. Moreover, cell-based assays should be considered as mandatory and mimicking as much as possible the in-vivo mechanism of action. Similarly, if a failure occurs in the binding assays like SPR, this could be translated in a different ability of the protein to bind the receptor in vivo. | Suggest removing lines 400-403 |
| 5 | 452-454 | The sentence, which is considering only hormones and enzymes, could be extended to all molecules having a certain level of glycosylation heterogeneity. | Products such as recombinant hormones and, enzymes AS WELL AS MABS AND IG-FUSION PROTEINS may have complex glycosylation profiles and multiple N-linked and O-linked sites of glycosylation See: van Bueren, J., Rispens, T., Verploegen, S. et al. Anti-galactose-α-1,3-galactose IgE from allergic patients does not bind α-galactosylated glycans on intact therapeutic antibody Fc domains. Nat Biotechnol 29, 574–576 (2011). https://doi.org/10.1038/nbt.1912 |
| 6 | 456-470 | Although not part of the similarity assessment, process related impurities and contaminants should also be addressed (see also comments to lines 252-265). | |

| | | | |
|---|---|---|---|
| 7 | 470-471 | Accelerated and stress stability studies, as well as forced degradation studies, should be used to establish degradation profiles and to provide a direct stability comparison of the proposed product with the reference product over time, with potential impact on safety and efficacy, in view to further harmonize with FDA requirements (Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry \| FDA). https://www.fda.gov/regulatory-information/search-fda-guidance-documents /development-therapeutic-protein-biosimilars-comparative-analytical-assessment-and-other-quality | Accelerated and stress stability studies, as well as forced degradation studies, SHOULD be used to establish degradation profiles and to provide a direct stability comparison of the proposed product with the reference product over time, with potential impact on safety and efficacy. |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| | | | |

| | | | |
|---|---|---|---|
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.1.8 Final reflection on Quality aspects

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 472-489 | We would recommend to rather provide clarity and examples for when a CES would be needed in accordance with 3.1.2 and 3.1.7 and related comments for these sections. | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |

| | | | |
|---|---|---|---|
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

## 2.3.2. Clinical

### 2.3.2.1 Utility and Limitations of Comparative Clinical Efficacy/Safety Trials

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 501-507 | It is proposed that the important considerations in lines 501-507 are mentioned in the Introduction section and further expanded (see comments to lines 163-173 and lines 310-364). For example, what specific scientific factors/considerations will be used to determine that “a biological is not well-characterizable and/or has an unknown or poorly understood MoA, structure-function relationship, or the impact of observed differences on clinical outcomes is unclear” and at what stage will this determination be made to inform the need for more extensive clinical evaluation of the biosimilar. | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |

| | | | |
|---|---|---|---|
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.2.2 The relevance of pharmacokinetic (PK) studies in biosimilar development

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 527-530 | This sentence argues that a PK study cannot draw robust conclusions on safety. This is supported. However, it contradicts the statement in lines 531-532 that states that the comparative PK study can address residual uncertainty related to safety. | |
| 2 | 533-534 | Cases where a CES should be conducted goes beyond this statement. These include cases – for example – where the mechanism of action is not fully understood, cases with heterogeneity or insufficient characterisation of structure and cases with high immunogenicity risk. It is recommended to provide more details in section 3.1.2 on risk-based criteria as to when a CES will be needed and to consider developing a decision tree (to be included in an Annex) on how to handle residual uncertainties accompanied by illustrative examples. | Please make reference to sections 3.1.2 and 3.1.7 (with proposal for a decision tree in an Annex). |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| | | | |

| | | | |
|---|---|---|---|
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### *2.3.2.3 Pharmacodynamics (PD)*

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 541 | It should be noted that relevant PD endpoints – in some cases – should be investigated in a relevant patient population and not in healthy participants. | Propose adding after ...and therapeutic potential: PD ENDPOINTS SHOULD - IN SOME CASES - BE INVESTIGATED IN A RELEVANT PATIENT POPULATION AND NOT IN HEALTHY PARTICIPANTS. |
| 2 | 548-553 | Biological medicines encompass a very diverse group of molecules ranging from relatively simple peptides to highly complex proteins such as bispecific antibodies. The section – as it currently reads – does not sufficiently address the more complex biologics where reliance on PK alone or PK combined with PD markers is clearly not sufficient and where CES is still needed. In addition to the comments in the right column, it is proposed that the section provides more details on situations where: a PK studies alone without PD markers and CES may be sufficient; b. PK study combined with PD markers will be | Suggest adding after line 547: HOWEVER, IN CASES WHERE THERE IS UNCERTANTY IN THE TRANSLATABILITY OF ANALYTICAL ENDPOINTS, WELL-ESTABLISHED PD MARKERS THAT CAPTURE THE MECHANISM OF ACTION AND MECHANISM OF TOXICITY ARE NEEDED. Suggest revising as follows: "Nonetheless, even if not essential, PD comparability evaluations may provide additional layers of confidence and assurance in the biosimilar's clinical performance." If relevant PD endpoints can be easily measured within the PK study (E.G., THE PD READ OUT IS NOT SATURATING THE DOSE RESPONSE CURVE) AND ARE ACCEPTED AS VALID SURROGATE ENDPOINTS (I.E., THERE IS EVIDENCE THAT THEY WOULD REFLECT THE MECHANISM OF ACTION AND THE RELATED CLINICAL OUTCOME), applicants SHOUL INCLUDE them. If an equivalence criterion has to be fulfilled also for the PD endpoints, this needs to be considered in the sample size calculation of the PK/PD study. It should be considered that PD endpoints may not be meaningfully interpretable or sensitive enough in healthy volunteers. Suggest adding: FOR BIOLOGICS WITH COMPLEX MECHANISMS OF ACTION (SUCH AS BISPECIFIC T-CELL ENGAGERS OR |

| | | | |
|---|---|---|---|
| | | adequate; and c. CES will be necessary. Please also see earlier comments on including a decision tree in an Annex. | MULTISPECIFIC BIOLOGICS IN CANCER IMMUNOTHERAPY), MECHANISM-RELATED PD-EFFECTS RELEVANT TO EFFICACY MAY BE DIFFICULT TO QUANTITATIVELY EVALUATE IN CIRCULATION OR PREDICT FROM PK ASSESSMENTS ALONE. WHILE TUMOR PD ASSESSMENTS ARE USED FOR INFORMING THE DEVLOPMENT OF SUCH AGENTS, THEIR APPLICABILITY IN THE CONTEXT OF BIOSIMILARITY ASSESSMNENT IS NOT STRAIGHTFORWARD, FURTHER ADDING UNCERTAINTIES IN DEMONSTRATING SIMILARITY IN DRUG EFEFCTS RELEVANT FOR EFFICACY AT THE SITE OF ACTION. FOR SUCH PRODUCTS, WAIVING CES WOULD BE QUESTIONABLE. |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |

| | | | |
|---|---|---|---|
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

**2.3.2.4 Safety and Immunogenicity**

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | 558-576 | Immunogenicity remains a critical concern in biosimilar development, especially for more complex biologics but sometimes even for smaller peptides. The formation of anti-drug antibodies (ADAs) can have significant implications for patient safety, yet PK studies often do not include a sufficient number of participants to adequately assess the immunogenicity risk, especially when the incidence is low. While section 3.2.4.1 acknowledges that in some cases, immunogenicity data from a single-dose PK study may not be enough, it fails to adequately address how immunogenicity can be | Suggest revising lines 558-576 as follows: IMMUNOGENICITY REMAINS A CRITICAL CONERN IN BIOSMILAR DEVELOPMENT, ESPECIALLY FOR MORE COMPLEX BIOLOGICS. THE FORMATION OF ANTI-DRUG ANTIBODIES (ADAS) CAN HAVE SIGNIFICANT IMPLICATIONS TO PATIENT SAFETY. While comparative PK studies primarily focus on establishing equivalence in drug exposure between the biosimilar and the reference medicinal product, they "can" MAY also provide supportive safety and immunogenicity data that help ascertain similarity in immunological responses between the biosimilar and the reference medicinal product. In cases with a comprehensive quality package showing close analytical similarity and high purity of the biosimilar, a "limited but" well-defined set of comparative safety and immunogenicity data as part of the PK study could provide sufficient confidence in the biosimilar's safety and immunogenicity profile. "If relevant uncertainties remain from the quality package, longer and/or larger studies may be needed to ensure the absence of a clinically relevant impact. In case relevant uncertainties remain, longer and/or larger studies may be needed to ensure no clinical meaningful impact (see also 3.1.7.5, 3.1.7.6.). 3.2.4.1. Extended PK studies with more than one dosing In some cases, immunogenicity data from a single-dose PK study may not be enough, especially if anti-drug antibodies (ADAs) are known to exert relevant effects on efficacy (e.g., due to neutralising antibodies) or safety (e.g., serious infusion reactions) developing later in the treatment course. In such cases, two or even |

| | | | |
|---|---|---|---|
| | | meaningfully investigated in a PK study that would risk being too small in terms of treatment duration (number of administrations) and number of participants to investigate immunogenicity in a meaningful manner. It also does not recognize the need for a PK study to be conducted in an appropriately sensitive population to detect safety or immunogenicity concerns. | more administrations may be necessary in an appropriate healthy volunteer or patient population. The applicant should assess the timeframe of ADA development and the immunogenic risk of the reference medicinal product to design a comparative PK study of adequate duration." HOWEVER, IMMUNOGENICITY DATA FROM A SMALL-SCALE SINGLE-DOSE PK STUDY WILL OFTEN NOT BE SUFFICIENT, AND EXTENDED PK STUDIES EMPLOYING MULTIPLE DOSES AND A LARGER NUMBER OF PARTICIPANTS SHOULD BE CONSIDERED. FACTORS SUCH AS THE IMMUNOGENICITY RISK OF THE REFERENCE PRODUCT, TIMEFRAME OF ADA DEVELOPMENT, CLINICAL CONSEQUENCES OF ADA FORMATION, POTENTIAL CROSS-REACTIVITY TO ENDOGENOUS LIGANDS AS WELL AS REMAINING UNCERTAINTIES FROM THE QUALITY PACKAGE SHOULD BE CONSIDERED. IN SOME CASES, MEANINGFUL IMMUNOGENICITY DATA CANNOT BE DERIVED FROM A PK STUDY, AND A DEDICATED CLINICAL SAFETY AND IMMUNOGENICITY STUDY (OR CES WITH IMMUNOGENICIITY ASSESSMENTS) WILL BE NEEDED. THE MOST SENSITIVE , IMMUNOCOMPETENT POPULTION SHOULD BE USED FOR THE EVALUATION, WHICH IS NOT ALWAYS HEALTHY VOLUNTEERS. |
| 2 | 558-568 | The paper does not provide direction or factors for consideration regarding what amount and duration of safety evaluation EMA expects to be collected in a PK similarity study for a biosimilar program where no CES is conducted. To date, EMA has generally expected 12-months of safety data to be collected for a biosimilar | |

| | | | |
|---|---|---|---|
| | | development program, which is generally beyond the primary endpoint for a PK similarity study. Clarity on expectations and factors for determination amount and duration of safety evaluation should be provided. | |
| 3 | Before Conclusion | There is no section on the CES in the reflection paper. | It is proposed to insert a short section on Comparative Efficacy Studies (CES) and in this section make reference to the EMA guideline “Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues” as well as product-specific biosimilar guidelines. |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |

| | | | |
|---|---|---|---|
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

### 2.3.3 Conclusion

### *2.3.3 Conclusion*

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

## 2.4 References

## 2.4 References

| | Line number(s) of the relevant text *(e.g. 20-23)* | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | |
| 20 | | | |
| 21 | | | |
| 22 | | | |
| 23 | | | |
| 24 | | | |
| 25 | | | |
| 26 | | | |

| | | | |
|---|---|---|---|
| 27 | | | |
| 28 | | | |
| 29 | | | |
| 30 | | | |

## 2.5. List of abbreviations

**2.5 List of abbreviations**

| | Line number(s) of the relevant text (e.g. 20-23) | Comment and rationale | Proposed guidance text |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | | | |
| 15 | | | |

# Thank you

Thank you for your contribution.


## Contact

Contact Form