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

Fields marked with * are mandatory.

* Name of organisation or individual

Alliance for Safe Biologic Medicines

* Country of organisation or individual

United States of America

* Email

ray@safebiologics.org

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".

Michael Reilly and Ralph McKibbin, MD

Please click here to be redirected to the guideline text. The public consultation is launched on 1 February 2024 until 30 April 2024.

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. 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 April 2024) 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.

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 questionnaire 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.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

Complaints

If you have any complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@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 Statement above and that you consent to the processing of your personal data.

- (●) Yes
- ( ) No

* 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.

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.

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

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1. General comments on the Concept paper for the development of a Reflection Paper on a tailored clinical approach in Biosimilar development

	Stakeholder name *(to be repeated in all rows)*	General comment
		ASBM is an organization of patient advocacy organizations, physicians, pharmacists, researchers, and manu-facturers of both originator biologics and biosimilars; working together to promote the appropriate use of biosimilars globally. Since 2010, ASBM has partnered with national regulatory authorities worldwide (includ-ing the EMA, FDA, Health Canada, the WHO, the Australian TGA, ANVISA, the Spanish and Italian Health Ministries) to share patient and physician perspectives and promote patient-centered policies. Europe's existing biosimilar pathway has been success-ful in building physician confidence. In 2019, ASBM conducted a survey of 579 physicians across France, Ger-many, Italy, Spain, Switzerland, and the UK, all of whom prescribe biologics. This survey revealed that 84% were comfortable prescribing a biosimilar to a new/naïve patient. We believe that clinical data, including comparative effectiveness studies (CES), have played a critical role in building physician and patient confidence in biosimilars and should continue to be required for complex biosimilars such as monoclonal antibodies. CES are critical because they provide direct evidence of how a biosimilar works in humans. They demonstrate real, not merely theoretical safety and efficacy in a wide variety of pa-tients. CES also helps address individual patient varia-bility. Replacing the current, highly successful approval stand-ards could undermine this success, potentially causing physicians to be less accepting of newer biosimilars approved under the lower standard, and instead preferen-tially prescribe the reference product or earlier biosimilars approved under the previous, more robust standards.

1	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	Similarly, the change may have unforeseen negative effects on patient confidence in biosimilars. Knowing that a biosimilar has undergone thorough clinical test-ing to demonstrate its safety and effectiveness can be reassuring for patients, especially those switching from a well-established biologic therapy. It is conceivable that a mass nocebo effect could be produced across many patient populations by these regulatory changes, stemming from patient uncertainty over reduced clini-cal testing requirements and lowered approval stand-ards driven by cost-cutting and desire for speedier approval. In addition, certain patient groups, such as those with complex chronic conditions, might be more sensitive to minor differences between biologics and their biosimi-lars. Without thorough clinical testing, it may be chal-lenging to understand fully the impacts in these sub-groups. ASBM believes the doctor-patient relationship itself is built on the foundation of trust created by a rigorous and reviewable evaluation process. This relationship should be fostered through robust and transparent ap-proval processes. For example, clinical effectiveness studies have been central to evaluation and approval of medications, and this process has evolved with time to decrease the ef-fect of bias. New technologies have been included in CES but have undergone extensive validation. New as-says and tests generally require reproducibility in other independent laboratories prior to acceptance. The crite-ria used for making such judgements are subject to open peer review and analysis; proprietary testing and judgement criteria are not generally acceptable. CES results are transparent and open to review- any pro-posed new evaluation scheme that de-emphasizes CES must be made equally transparent and reviewable by outside independent reviewers in order to maintain physician and patient trust. Similarly, implementation of an evaluation scheme de-signed to speed

		approvals by minimizing CES creates many new challenges that would need to be addressed in a transparent manner in order to maintain stake-holder confidence: How will endpoint criteria be validated? How will these criteria change or evolve? How will subjective opinion be minimized or eliminated? Managerial and scientific criteria can be discordant; how will these inevitable conflicts of interest be elimi-nated? What role, if any, will third party outside review of decision making play; and how will this be determined? The EMA leads the world in biosimilar development and commercialization. Biosimilar uptake rates and physi-cians confidence are high across European member states. We believe this success is due in large part to the EMA's commitment thus far to robust approval standards reliant on CES. For these reasons, we urge the CHMP to act cautiously and not risk jeopardizing these successes of the EMA's biosimilar program by inappropriately reducing the role of CES in biosimilar approvals.
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2. Specific comments on text

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	20-21	McKibbin, MD; Alliance for Safe Biologic Medicines	“the importance of dedicated clinical efficacy….should be re-evaluated”. It is important to note that this is not a unanimous view. Patient advocacy organizations, healthcare providers, and manufacturers have emphasized in their comments the importance of clinical data particularly when involving switching patients from one biologic to a biosimilar or between two biosimilars.	“Some believe the importance of dedicated clinical efficacy….should be re-evaluated. Many stakeholders disagree and urge caution so as not to undermine hard-won confidence in biosimilar safety and efficacy among physicians and patients”.
2	21	McKibbin, MD; Alliance for Safe Biologic Medicines	“Currently, the need for Comparative Efficacy Studies (CES) is increasingly questioned in general.” EMA should aim to preserve phy-sician confidence and avoid hesitancy among prescribers to prescribe newer biosimilars approved under the lower evaluation standards, and avoid producing nocebo effects in patients on these products due to percep-tions of lowered standards. Evaluation of molecular evidence for the active ingredient is only part of the picture. The novel statistical methods may show equivalence of ingredient levels but effectiveness complexity is increased by such things as using long acting preparations, biodiversity of patients and binding to sites other than that of the mechanism of action.	“Currently, the need for Comparative Efficacy Studies (CES) is increasingly questioned in general. Nevertheless, it may still be scientifically appropriate when dealing with complex biosimilars such as monoclononal antibodies; this will help maintain confidence in biosimilars among physicians and patients."

3			CES shows effectiveness. Analytic methods are evolving and public access to criteria are not available. Confidence will require commitment to adverse event tracking and pharmacovigilance.	
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2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	31-34	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“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.” The constant evolution of development processes requires constant assessment of testing and evaluation criteria. CES evolution has been towards outside blinded and peer review. The doctor patient relationship for decision making is based on this. How will these processes be validated?	“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. Nevertheless, the constant evolution of development processes has been toward outside blinded and peer review of testing and evaluation criteria and this pattern must be preserved in order to maintain physician and patient confidence; particularly for more complex molecules.”
2	35-37	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“revisiting the need for clinical efficacy trials for biosimilars (especially recombinant proteins and mAbs) is considered the next important step” – update to reflect this is not a unanimous view.	“revisiting the need for clin-ical efficacy trials for bio-similars (especially recom-binant proteins and mAbs) is considered BY SOME to be the next important step”

3	37	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“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” Keeping the pathway attractive for developers is a sub-jective evaluation. Investment of resources is complicated and based on many issues such as number of competitors, market share, potential market, etc and will vary widely. Certainly access to drugs is critical but changing evaluation criteria due to market pressures is a potential conflict of interest and can create uncertainty and reduce confidence.	“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 without undermining physician and patient confidence in the biosimilar evaluation processes”
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2.3 Discussion (on the problem statement)

	Description of the element of the figure	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text / element of the figure
1	47	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“it may be possible to justify the omission” – then again, it may not.	“it may or may not be possible to justify the omission…”
2	48-49	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“This approach aims to streamline the development and evaluation process while maintaining the highest standards of safety and efficacy.” – this neglects the role of clinical data in building physician and patient confidence, and in patient response to the medicines (nocebo effect, etc).	This approach aims to streamline the development and evaluation process, while maintaining the highest standards of safety and efficacy, and without negatively impacting physician and patient confidence in and perceptions of future biosimilars relative to those approved with CES.
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2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	63-64	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“CHMP acknowledges the possibility for further tailoring of the clinical approach for biosimilars..” – There may be a possibility, but there is not a certainty that this will be appropriate in all or even most cases.	“CHMP acknowledges there may be the possibility for further tailoring of the clinical approach for biosimilars IN CERTAIN CASES, WHEN APPROPRIATE”
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2.5 Proposed timetable

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6 Resource requirements for preparation

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2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	81-82	Michael Reilly and Ralph McKibbin, MD; Alliance for Safe Biologic Medicines	“The Reflection Paper will outline current thinking on the need for CES with a view to improving the efficiency of biosimilars development. “ Current thinking should also include stakeholder concerns. Access to medications goes beyond production and mechanisms to reduce erosion of confidence are critical. Transparency is needed.	“The Reflection Paper will outline current thinking, including stakeholder perspectives and any concerns, on the need for CES with a view to improving the efficiency of biosimilars development. “
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2.8 Interested parties

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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Thank you for your contribution.

Contact

Contact Form