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Streamlining Development Of Biosimilars

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AAM Generics + Biosimilars conference
October 21-24, 2024
Bethesda

Biocon Biologics has acquired the global biosimilars business of Viatris to become a unique, fully integrated, leading global biosimilars player.

Transforming Healthcare. Transforming Lives.

Criteria by which manufacturers may ask for a waiver of the comparative efficacy study

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When a controlled efficacy study (CES) is needed (MHRA) and when not (WHO)	
MHRA: When CES may be needed (2020)	**WHO: When CES may not be needed (2022)**
• Lack of understanding of the biological functions of the RP related to its clinical effects. • The relevant Critical Quality Attributes cannot be sufficiently characterized due to analytical limitations. • Exceptionally, where safety uncertainties cannot be resolved without patient exposure pre-licensing.	• The mechanism of action in different indication is known and can be investigated by binding and functional in vitro test. • The biosimilars can be sufficiently characterized analytically and functionally to demonstrate similarity. • The existence of a relevant pharmacodynamic parameter. • Knowledge of no unwanted immunogenicity, as with erythropoietin and coagulation factors. • The impurity profile or the excipients of the biosimilars do not rise clinical concerns.

ADRs: adverse drug reactions, MHRA: Medicines and Healthcare products Regulatory Agency; RP: Reference product; WHO: World Health Organization

Pekka Kurki September 2024, https://gabi-journal.net/comparative-efficacy-studies-of-biosimilars-data-versus-theoretical-risks-beliefs-and-comfort.html?print

Streamlining Development Of Biosimilars

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Regulatory Landscape FDA and EMA Status Quo

	Fine as is ?	Comment
EU Directive	Yes	The current directive is in principle flexible enough to allow streamlining.
FDA guidelines EU CHMP guidelines	No Streamlining is discouraged	Change in FDA guidelines and Revised CHMP guidelines on nonclinical and clinical considerations are desirable to enable investments in streamlined devlopments
FDA BIAM/Typ 2 EU Scientific Advice procedure	Not sufficiently clear Slow process	Many scientific advice procedures repeat past thinking or are vague in outlook → Need paradigm shift The intention of Scientific Advice should be revised to be clear on expectations that enable streamlined programs

Regulatory insights are evolving: The EMA papers in 2023

1. A data driven approach to support tailored clinical programmes for biosimilar monoclonal antibodies

Elena Guillen Niklas Ekman , Sean Barry Martina Weise Elena Wolff-Holz
Clin Pharmacol Ther, Jan 2023 ;113(1):108-123.
doi: 10.1002/cpt.2785

2. Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars?

Nadine Kirsch-Stefan, Elena Guillen, Niklas Ekman, Sean Barry, Verena Knippel, Sheila Killalea, Martina Weise, Elena Wolff-Holz
BioDrugs. 2023 Nov;37(6):855-871.
doi: 10.1007/s40259-023-00631-4.

1. Comparative Efficacy Study (CES) and
2. The clinical part of the MAA dossier were not predictive for the MA of biosimilars in the EU

→ Quality/CMC part of the dossier was predictive

Comparative Efficacy Studies (CES) were not predictive for the marketing authorization of biosimilars in the EU

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Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 1	**IgG type**	**Date of MA**	+	+	+	+
Infliximab 1	IgG1	10/09/2013				
Infliximab 2	IgG1	26/05/2016				
Infliximab 3	IgG1	18/05/2018				
Etanercept 1	Mod. IgG1	13/01/2016				
Etanercept 2	Mod. IgG1	23/06/2017				
Adalimumab 1	IgG1	21/03/2017				
Adalimumab 2	IgG1	24/08/2017				
Adalimumab 3	IgG1	17/09/2018				
Adalimumab 4	IgG1	02/04/2019				
Adalimumab 5	IgG1	13/02/2020				
Adalimumab 6	IgG1	11/02/2021				
Adalimumab 7	IgG1	15/11/2021				
Rituximab 1	IgG1	15/06/2017				
Rituximab 2	IgG1	13/07/2017				
Rituximab 3	IgG1	01/04/2020				
Bevacizumab 1	IgG1	15/01/2018				
Bevacizumab 2	IgG1	14/02/2019				
Bevacizumab 3	IgG1	19/08/2020				
Bevacizumab 4	IgG1	24/09/2020				
Bevacizumab 5	IgG1	26/03/2021				
Bevacizumab 6	IgG1	21/04/2021				
Bevacizumab 7	IgG1	17/08/2022				
Trastuzumab 1	IgG1	09/02/2018				

29/36 MAAs: quality and clinical data supportive and aligned

BioDrugs. 2023 Nov;37(6):855-871.

Analysis of MAA outcome

Cases			Quality		Clinical	
			biosimilarity	general Q	PK/PD	E/S/I
SCENARIO 2	**IgG type**	**Date of MA**	-	-	+	+
Rituximab 4	IgG1	not approved				
Trastuzumab 5	IgG1	not approved				
SCENARIO 3	**IgG type**	**Date of MA**	+	+	-	+
Adalimumab 8	IgG1	10/11/2017				
Adalimumab 9	IgG1	26/07/2018				
Etanercept 3	Mod. IgG1	20/05/202				
SCENARIO 4	**IgG type**	**Date of MA**	+	+	+	-
Trastuzumab 6	IgG1	15/11/2017				
Trastuzumab 7	IgG1	16/05/2018				
SCENARIO 5	**IgG type**	**Date of MA**	-	-	-	-

2/36 MAAs: Quality was unconvincing but clinical trial was successful

5/36 MAAs: Quality was convincing with uncertainties in clinical which were resolved

The Quality/CMC part of the dossier was predictive for the marketing authorization of biosimilars in the EU

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Analysis of first regulatory assessment; All biosimilar mAbs and fusion proteins evaluated by the EMA between July 2012 and November 2022

Case	Quality MO	Clinical MO		% of biosimilar candidates applicable to each case*
		PK/PD	E/S/I	
1				42
2				11
3				22
4				25

- In 22% of cases, Major Objections were raised on the clinical data package but not on the quality data
- In no instance this seemingly negative clinical data, including failed efficacy trials, led to a negative overall decision

BioDrugs. 2023 Nov;37(6):855-871.

Regulatory insights are evolving: The FDA papers in 2023 and 2024

80 biosimilar applications received by FDA
16 have received notices their application cannot be approved in the present form

Analytics:

6 of those 16 included a concern, based on the **Comparative Analytical Analysis** (CAA), that the biosimilar may not be "highly similar" to the reference product.

Clinical studies

- In only 1 of these 6 applications did the results of a clinical efficacy study also indicate a potential concern.
- **In NO application did clinical studies detect a potential issue that was not also detected by the CAA**.
- This reflects the CAA's fundamental role in serving as a more sensitive evaluation for potential differences between biosimilars and their reference products.

Cavazzoni P, Yim S.
The Science of Biosimilars— Updating Interchangeability. JAMA. Published online September 18, 2024.
doi:10.1001/jama.2024.15225

Regulatory insights are evolving: The FDA papers in 2023 and 2024

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"As familiarity with and understanding of the rigor of the analytical comparisons used to support biosimilar approvals increases,

the amount and types of clinical data routinely performed as part of biosimilar development may be reduced,

which in turn would reduce the time and cost of development."

Herndon T, Ausin C, Brahme N, Schrieber S, Luo M, Andrada F, Kim C, Sun W, Zhou L , Grosser S, Yim S, Ricci S; Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis

IPRP Biosimilars Working Group (BWG) in 2023

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Workshop Summary Report: Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies

Multiple stakeholders expressed that successful functional characterization using in vitro bioassays may preclude the need for a CES, in part due to the high specificity and sensitivity of these functional characterization assays for detecting clinically meaningful differences.

→ If a CES is to be used, it should be designed purposefully to answer a specific question that cannot be addressed from the comparative functional characterization.

Conclusions

- Regulatory insights are evolving with convergence of thinking between regulatory bodies (MHRA, WHO, EMA, FDA, IPRP) observed.
- Further need to future proof legislation and biosimilar guideline requirements as technology has progressed.
- Well established regulatory science supports the development of biosimilars based on Comparative Analytical Analysis plus a clinical pharmacokinetic study, which includes safety and immunogenicity data.
- Any study involving human subjects must take particular care to contribute new knowledge not otherwise obtainable.
- If a Clinical efficacy study (CES) is to be used, it should be designed purposefully to answer a specific question that cannot be addressed from the comparative functional characterization.
- A modern biosimilar pathway ensures broader access of biologicals to patients while stimulating competition and innovation.

References

MHRA (UK)

- Bielsky et al. Drug Discov. 2020; 25, 1910-1918 doi: https://doi.org/10.1016/j.drudis.2020.09.006
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WHO

- World Health Organization. Guidelines on evaluation of biosimilars. Replacement of annex 2 of WHO technical report series, no.977. 2022 : https://www.who.int/publications/m/item/guidelines-on-evaluation-of-biosimilars

EMA

- Concept paper that proposes drafting a reflection paper for re-evaluation of the need for comparative efficacy studies https://www.ema.europa.eu/en/documents/other/concept-paper-development-reflection-paper-tailored-clinical-approach-biosimilar-development_en.pdf
- Guillen, E. et al, Clin Pharmacol Ther, Jan 2023 ;113(1):108-123
- Kirch-Stefan, N. et al BioDrugs, 2023 Nov;37(6):855-871.

FDA

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IPRP

- IPRP Biosimilar Working Group (BWG) Report: Increasing the Efficiency of Biosimilar Development Programs — Reevaluating the Need for Comparative Clinical Efficacy Studies. IPRP_BWG_Final IPRP Scientific Workshop Summary Report_2024_0506.pdf

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Thank you