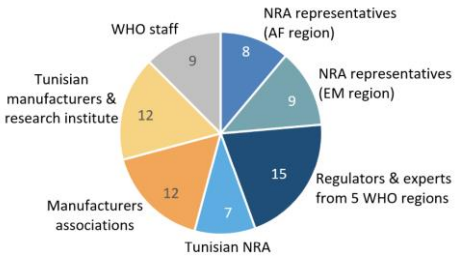
WHO Implementation Workshop:
Revised WHO Guidelines on Evaluation of Biosimilars
26–28 November 2025, Tunis, Tunisia

Background and objectives

The WHO implementation workshop on the revised WHO guidelines on evaluation of biosimilars was held from 26 to 28 November 2025 in Tunis, Tunisia as a hybrid meeting. The workshop was attended by 72 participants (51 in-person, 21 virtually connected) including representatives from national regulatory authorities (NRAs) in the African and Eastern Mediterranean regions, regulatory experts from 5 WHO regions, the Tunisian NRA, manufacturers' associations, Tunisian manufacturers and research institute, as well as WHO staff.

The workshop aimed to support implementation of the revised WHO biosimilar guidelines (WHO TRS 1043, Annex 3, 2022), strengthen regulatory capacity, and promote convergence toward science-based biosimilar evaluation. Through technical presentations, case-study exercises, and stakeholder discussions, participants gained practical understanding of the streamlined approach and its application. A detailed agenda of the workshop is provided at the end of this document.

(a) Countries of participating regulators/experts



(b) Participants composition

Key themes and technical discussions

1. Global evolution of biosimilar evaluation

Participants reviewed scientific and regulatory developments since the first WHO guidelines in 2009 that led to the revision in 2022. Advances in analytical and functional technologies, together with accumulated regulatory experience have demonstrated that analytical characterization is generally more sensitive than comparative efficacy studies (CES) for detecting differences between a biosimilar candidate and its reference product (RP). The revised guidelines harmonize terminology through universal use of 'biosimilar,' expand scope to well-characterized biological therapeutics, clarify expectations for the use of non-local reference products (RPs), statistical principles, and international standards. They emphasize that biosimilar development begins with comprehensive RP characterization to define quality attributes (QAs) and their criticality with regard to clinical performance, and guide biosimilar development such that a product that is analytically similar to the RP is manufactured, enabling streamlined clinical programs focused mainly on Pharmacokinetics/Pharmacodynamics (PK/PD) and immunogenicity.

(a) Quality Evaluation

Quality evaluation requires robust characterization of multiple RP batches to understand variability and establish similarity ranges for the different quality attributes. Use of sensitive physicochemical and functional methods including state-of-the-art and orthogonal methods is essential for RP characterization as well as for comparability studies between the RP and the biosimilar product in development. For each molecule, criticality of QAs is ranked by relevance to clinical performance in terms of impact on efficacy, PK/PD, safety, and immunogenicity, and any differences seen must be scientifically justified. The guidelines reiterate that biosimilars must meet the same quality standards as any biological product and that manufacturers must demonstrate strong product and process knowledge to ensure consistent product quality.

(b) Nonclinical Evaluation

The workshop highlighted the shift from routine animal studies to a risk-based approach relying primarily on analytical and functional data. Due to limited analytical sensitivity, in vivo studies, historically used, are now rarely needed and reserved for exceptional cases such as novel excipients. Significant differences in critical QAs cannot be compensated by non-clinical/clinical data and indicates clearly that a product does not meet biosimilarity criteria.

(c) Clinical Evaluation

Clinical requirements have evolved with CES no longer routinely required when robust analytical and functional similarity is demonstrated for well-characterized products with known mechanism of action. PK studies potentially including PD endpoints and supported by targeted immunogenicity assessments typically provide sufficient clinical evidence. This case-by-case, evidence-based approach aligns with global regulatory convergence, including ICH M18.

2. Case Studies: Application of the Revised Principles

Two case studies helped participants apply some of the concepts from the revised framework. The insulin analogue case demonstrated how analytical, functional, purity, and stability data support similarity conclusions for biological products with low structural complexity.

The anti-TNFα monoclonal antibody case illustrated the complexity of evaluating multifunctional biologics, focusing on glycosylation, potency, aggregation, and Fc-effector functions. Participants explored the ranking of criticality of QAs according to their functional impact, considered when PK/PD and immunogenicity data can replace CES, and recognized that major differences in critical QAs must be addressed through manufacturing process optimization rather than clinical justification.

3. Recent issues in biosimilar evaluation

(a) Recent developments

WHO International Standards (IS) were highlighted for supporting assay calibration, consistency of potency, harmonization of bioactivity across products and post-market surveillance. Examples highlighted the development of WHO IS such as adalimumab and showed how ISs can be used to detect and mitigate potency drift during product life-cycle management and for evaluation of falsified products.

The WHO Prequalification (PQ) program shared lessons from assessments of rituximab, trastuzumab, and insulin, noting improvements in dossier quality but ongoing challenges in comparability data, process understanding, and pharmacovigilance planning. Updated PQ guidance has been published, and

18 biotherapeutics have been prequalified. A human insulin Master File pathway was introduced to support broader global access.

The IPRP Biosimilars Working Group reported decreasing reliance on CES due to improved analytical tools. A white paper on risk-based CES decision framework is under development and expected in late 2025 or early 2026. A 2026 workshop will address harmonized criteria for non-local RPs and bridging requirements.

(b) Regulatory situation in AFR and EMR

A regional survey showed a diverse biosimilar landscape and uneven adoption of the revised WHO guidelines. Some countries reported mislabelled products marketed as biosimilars without adherence to WHO guidelines. NRAs continue to face constraints in technical expertise, comparability assessment, and resource capacity. Many NRAs rely on regional pathways such as ZAZIBONA[1], EAC-MRH[2], ECOWAS[3], AVAREF[4], and GCC[5] mechanisms. Regulators expressed strong interest in WHO support for training, harmonization, and regulatory strengthening.

(c) Industry perspectives

Industry associations expressed strong support for the revised WHO guidelines and confirmed broad integration into development programs. They emphasized the guidelines' clarity, science-based approach, and flexibility for waiving CES and animal studies. However, they noted that the full impact depends on consistent NRA adoption and clear differentiation between true biosimilars and non-comparable products.

Conclusions and next steps

Participants agreed that the revised WHO guidelines provide a clearer and more scientifically robust pathway for biosimilar development and assessment. The workshop enhanced practical understanding through case studies and open discussion. While the streamlined approach is feasible based on the different scenarios explored in the case studies, decisions must remain evidence-based and case specific. Countries requested continued WHO support through training, capacity building, and regulatory framework development. Participants suggested complementary learning modalities such as webinars and e-learning. Ongoing WHO facilitation of expert networks and scientific exchange will further advance regulatory convergence and expand global access to biological products of assured quality, safety, and efficacy.

[1] ZAZIBONA: Zambian, Zimbabwean, Botswana and Namibian (ZAZIBONA) Collaborative Medicines Registration Initiative
[2] EAC-MRH: East African Community-Medicines Regulatory Harmonization
[3] ECOWAS: Economic Community of West African States
[4] AVAREF: African Vaccine Regulatory Forum
[5] GCC: Gulf Cooperation Council

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AGENDA

Chair: M. Weise
Rapporteur: M. Wadhwa

Day 1 : Wednesday, 26 November

Session 1	**Welcome and introduction**	
09:00 – 10:00	Opening remarks and welcome by host	I. Knezevic, WHO
		S. Miled, ANMPS, Tunisia
	Group photo	
	Self-introduction	Participants
	Statement on DoI assessment	I. Knezevic, WHO
Session 2	**Background and objectives**	
10:00 – 10:20	Update on WHO biotherapeutic standardization activities	I. Knezevic, WHO
10:20 – 10:30	Objectives and expected outcomes of the meeting	E. Kim, WHO
10:30 – 11:00	***Coffee break***	
Session 3	**Revised WHO guidelines on evaluation of biosimilars[i]**	
11:00 – 11:20	Key updates: Scope and terminologies	H. Kang, WHO
11:20 – 11:45	Quality assessment	N. Ekman, FIMEA, Finland
11:45 – 12:00	Nonclinical evaluation	N. Jost, PEI, Germany
12:00 – 12:25	Clinical evaluation	M. Weise, BfArM, Germany
12:25 – 13:00	Discussion	
13:00 – 14:00	***Lunch break***	
Session 4	**Case studies on insulin biosimilars**	

14:00 – 14:30	Brief explanation of insulin and case studies	B. Kim , IFPMA, Eli Lilly & Co
14:30 – 16:00	Group work *(Participants divided into groups to discuss)*	
16:00 – 16:30	***Coffee break***	
16:30 – 17:20	Reporting of the outcomes	Rapporteur(or lead) from each group
17:20 – 17:50	Open discussion & summary	All participants
17:50 – 18:00	**Wrap-up of day 1**	Chair & Rapporteur

Day 2: Thursday, 27 November

Session 5	**Evaluation of biosimilars: Current practices & Regulator's perspective on WHO GLs**	
09:00 – 09:30	Feedback summary from countries	E. Kim, WHO
09:30 – 10:30	Roundtable discussion	All participants
10:30 – 11:00	***Coffee break***	
Session 6	**Evaluation of biosimilars: Current practices & Industry's perspective on WHO GLs**	
11:00 – 11:15	Current practices and IFPMA perspective on WHO GLs	I. Colmagne-Poulard, IFPMA, Merck
11:15 – 11:30	Implementation of WHO biosimilar GLs in the industry	T. Kirchlechner, IGBA, Sandoz
11:30 – 11:45	Applications of revised WHO GLs in biosimilar development	J. Ramalingam, DCVMN, Serum Institute of India
11:45 – 12:00	Current practices and perspective on WHO GLs from local manufacturers	A. Ganma, JAPM, MS Pharma
12:00 – 12:30	Discussion	
12:30 – 13:30	***Lunch break***	

Session 7	**Case studies on monoclonal antibodies biosimilars**	
13:30 – 14:00	Brief explanation of monoclonal antibodies and case studies	M. Schiestl, IGBA, Sandoz
14:00 – 15:30	Group work *(Participants divided into groups to discuss)*	
15:30 – 16:00	***Coffee break***	
16:00 – 16:50	Reporting of the outcomes	Rapporteur(or lead) from each group
16:50 – 17:20	Open discussion & summary	All participants
17:20 – 17:30	**Wrap-up of day 2**	Chair & Rapporteur

Day 3: Friday, 28 November

Session 8	**Evaluation of biosimilars: Recent news and issues**	
09:00 – 09:20	The role of WHO international reference standards throughout the product life-cycle	M. Wadhwa, MHRA, UK, H. Kang, WHO
09:20 – 09:40	IPRP BWG: Updates on the BWG Efforts in 2025	A. AlHomaidan, Saudi Arabia, Co-chair of IPRP BWG
09:40 – 10:00	WHO PQ: Updates on biosimilars evaluation	G. Pante, WHO
10:00 – 10:30	Discussion	
10:30 – 11:00	***Coffee break***	
Session 9	**Implementation of WHO Guidelines**	
11:00 – 12:00	Discussion: How to implement WHO Guidelines *e.g. implementation plan, tools to facilitate, support needed from WHO*	All participants
Session 10	**Conclusions and way forward**	
12:00 – 12:20	Summary report of points raised during the workshop	Chair & Rapporteur

12:20 – 12:25	Conclusions and next steps	Chair & Rapporteur
12:25 – 12:30	Closing remarks	I. Knezevic, WHO
12:30	**Close of the open meeting**	
12:30 – 13:30	***Lunch break***	
Session 11	**Closed session (regulators and participants without conflict of interest)**	
13:30 – 14:30	Report from countries: Country situation and progress made in the past 10 years	All NRAs
14:30 – 15:00	Discussion	
15:00	**Close of meeting**	

[i] WHO TRS 1043, Annex 3 (2022): https://iris.who.int/bitstream/handle/10665/362194/9789240057081-eng.pdf?sequence=1