SCOMRA 2025: Handout:
Dr Luther Gwaza, WHO

Session: Parallel V: Bioequivalence Centres and Regulatory Requirements

Title: Global perspective on BE regulation

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Generic medicines account for over 90% of all prescriptions filled in the United States[1], and about 70% of the medicine volume in Europe[2]. In Africa, where health systems rely heavily on generics for essential treatments, this proportion is likely even higher. Yet, Africa also bears the highest global prevalence of substandard and falsified medicines, estimated conservatively at around 10%. If we extrapolate from this, we must also recognize a hidden but equally serious problem: the risk of ineffective generics arising not from intent to falsify, but from inconsistent and poorly enforced requirements for demonstrating bioequivalence and therapeutic interchangeability.

Across the continent, manufacturers face divergent regulatory expectations on fundamental BE elements, such as how to select comparator products, when BE studies or biowaivers are required and how reviewers interpret data. These inconsistencies make it nearly impossible for an African manufacturer or any manufacturer to design a single, continentally or even globally acceptable development programme. More so, the variable capacity among BE centers in Africa leads to inconsistent execution. For regulators, limited expertise in BE assessment leads to inconsistent enforcement or unpredictable regulatory decisions, which undermines both confidence in generics and trust in regulatory systems.

Using WHO bioequivalence standards as a unifying framework, anchored in globally harmonized standards and demonstrated practical application through the WHO prequalification of medicines, Africa can ensure that the generic medicines reaching patients are truly interchangeable with innovators, while creating a predictable and harmonized environment for manufacturers. This toolkit includes WHO bioequivalence requirements, the List of International Comparator Products to support a single development programme, the WHO Biowaiver framework that defines when in vivo studies for specific products are not required, and product-specific study design issued by WHO prequalification. Complementing these are the WHO guidelines for BE centres or contract research organizations, which provide the technical pathway to meet international standards. Together, these instruments give countries and manufacturers a single, coherent foundation for demonstrating interchangeability, building regulatory confidence and accelerating patient access to affordable, quality-assured medicines.

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[1] Generic Drugs Market Size, Research, Trends and Forecast – Towards Healthcare, accessed July 28, 2025, https://www.towardshealthcare.com/insights/generic-drugs-market

[2] Beneath the Surface: Unravelling the True Value of Generic Medicines – IQVIA, accessed July 28, 2025, https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-true-value-of-generic-medicines-04-24-forweb.pdf

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List of WHO and other international scientific bioequivalence guidelines

Topic	Source / Reference	Source
Main BE guideline *(general requirements, BE for oral immediate, biowaiver for additional strengths, NTI)*	Annex 8: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. Geneva: World Health Organization; 2024:305-52 (WHO Technical Report Series, No. 1052, https://iris.who.int/handle/10665/376607).	WHO
Bioanalytical Method Validation and study sample analysis	Annex 6: Guideline on bioanalytical method validation and study sample analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-eighth report. Geneva: World Health Organization; 2025:307 - 62 (WHO Technical Report Series, No. 1060, https://iris.who.int/handle/10665/381072).	WHO
Selection of comparator products	Annex 8: Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015:185 - 9 (WHO Technical Report Series No. 992, https://iris.who.int/handle/10665/176954).	WHO
Selection of comparator products	Annex 5: General background notes on the list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017:179-80 (WHO Technical Report Series, No. 1003, https://iris.who.int/handle/10665/258720).	WHO
Selection of comparator products	**WHO/MHP/HPS/TSS/NSP/2024.2** – © WHO 2024. WHO List of International Comparator Products https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/current-projects/who_mhp_hps_tss_nsp_2024.2.xlsx?sfvrsn=efb0f02_3&download=true	WHO
BCS-based biowaivers	Annex 7: WHO guideline on Biopharmaceutics Classification System-based biowaivers. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-seventh report. Geneva: World Health Organization; 2024:279-304 (WHO Technical Report Series, No. 1052, https://iris.who.int/handle/10665/376607).	WHO
BCS-based biowaivers	Annex 5: WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for the WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-eighth report. Geneva: World Health Organization; 2025:293 - 306 (HO Technical Report Series, No. 1060, https://iris.who.int/handle/10665/381072).	WHO
BCS-based biowaivers	Annex 4: Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based	WHO

Topic	Source / Reference	Source
	classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019:203 - 18 (WHO Technical Report Series, No. 1019, https://iris.who.int/handle/10665/312316).	
Good clinical practice	Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report. Geneva: World Health Organization; 1995: (WHO Technical Report Series, No. 850, https://iris.who.int/handle/10665/42145).	WHO
CRO	Annex 9: Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016:305-46 (WHO Technical Report Series, No. 996, https://iris.who.int/handle/10665/255338).	WHO
CRO	Annex 7: Guidelines for the preparation of a contract research organization master file. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: (WHO Technical Report Series, No. 957, https://iris.who.int/handle/10665/44291).	WHO
Data integrity	Annex 4: Guideline on data integrity. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2021:135 - 59 (WHO Technical Report Series, No. 1033, https://iris.who.int/handle/10665/340323).	WHO
CRO inspections/reliance	Annex 9: Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018:271 - 307 (WHO Technical Report Series, No. 1010, https://iris.who.int/handle/10665/272452).	WHO
Pharmaceutical development	Annex 3: Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012:91 - 119 (WHO Technical Report Series No. 970, https://iris.who.int/handle/10665/75168).	WHO
Fixed-dose combination products	Annex 5: Guidelines for registration of fixed-dose combination medicinal products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005:94 - 142 (WHO Technical Report Series, No. 929, https://iris.who.int/handle/10665/43157).	WHO

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Structure and content of clinical study reports	ICHE3 Structure and Content of Clinical Study Reports. https://database.ich.org/sites/default/files/E3_Guideline.pdf ICHE3 Structure and Content of Clinical Study Reports. Questions and Answers (R1) https://database.ich.org/sites/default/files/E3_Q%26As_R1_Concept_Paper.pdf	ICH
Statistical principles for clinical trials	ICHE9 Statistical principles for clinical trials. https://database.ich.org/sites/default/files/E9_Guideline.pdf Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. E9(R1) https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf	ICH
General considerations for clinical studies	General considerations for clinical studies. E8(R1) https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf	ICH
Product Specific Guidelines	WHO Prequalification Product-specific guidance: https://extranet.who.int/prequal/medicines/who-medicines-prequalification-guidance Product-specific guidance from some regulators: *EMA product-specific guidance:* https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/product-specific-bioequivalence-guidance *US FDA product-specific guidance:* https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm	WHO PQ and specific NRAs