# Prequalification Team – Medicines (PQT/MED)

# Bioequivalence Assessment Update

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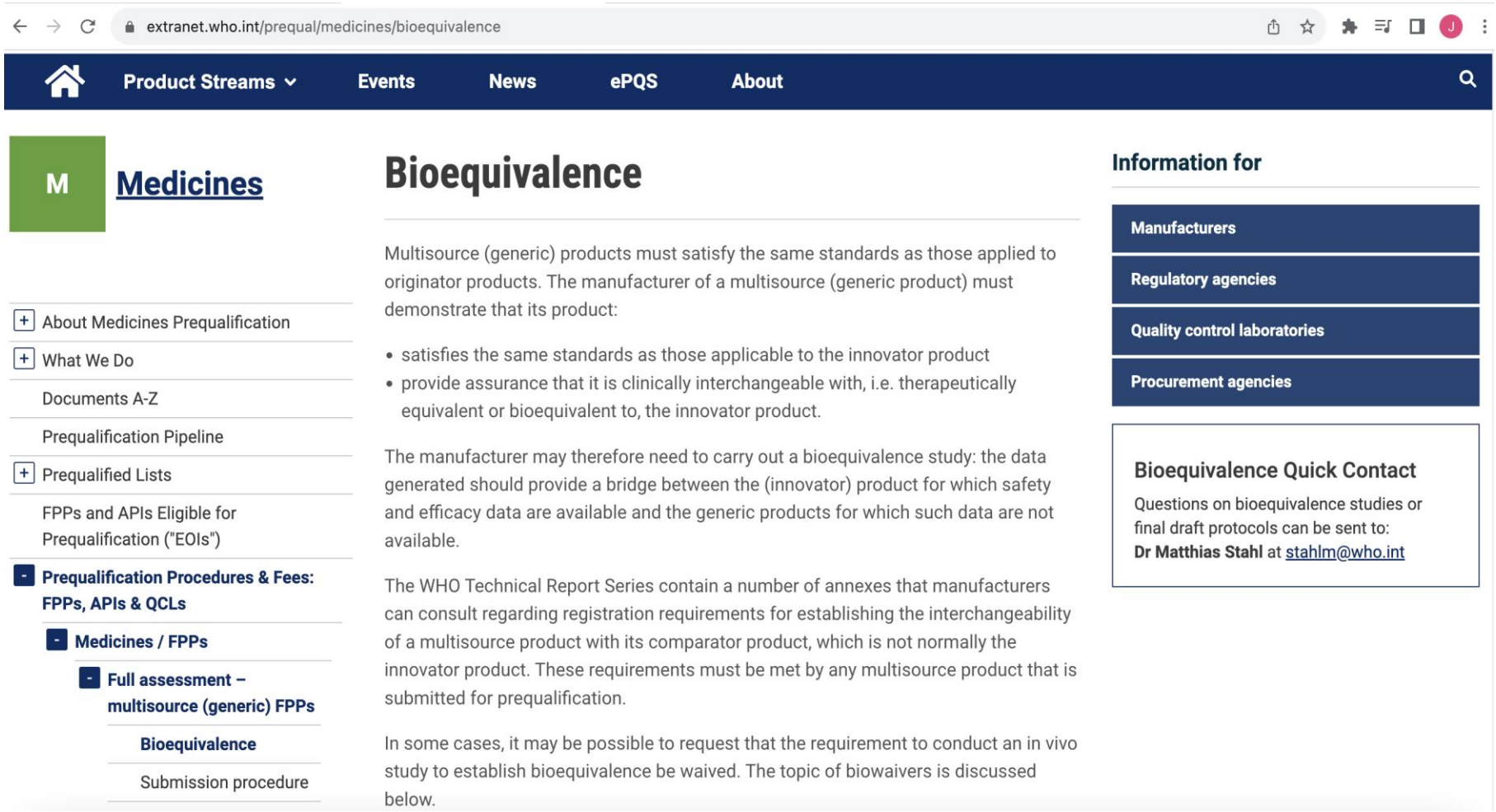
# Overview

- Bioequivalence guidance
- Notes on the design of bioequivalence study
  - Product specific guidance
- Recently invited products
- Comparator products
- BCS-based biowaivers
- Bioanalysis of BE study samples
- Bioequivalence Trial Information Form (BTIF)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Bioequivalence
Multisource (generic) products must satisfy the same standards as those applied to originator products. The manufacturer of a multisource (generic product) must demonstrate that its product:
satisfies the same standards as those applicable to the innovator product
provide assurance that it is clinically interchangeable with, i.e. therapeutically equivalent or bioequivalent to, the innovator product.
The manufacturer may therefore need to carry out a bioequivalence study: the data generated should provide a bridge between the (innovator) product for which safety and efficacy data are available and the generic products for which such data are not available.
The WHO Technical Report Series contain a number of annexes that manufacturers can consult regarding registration requirements for establishing the interchangeability of a multisource product with its comparator product, which is not normally the innovator product. These requirements must be met by any multisource product that is submitted for prequalification.
In some cases, it may be possible to request that the requirement to conduct an in vivo study to establish bioequivalence be waived. The topic of biowaivers is discussed below.
Information for
Manufacturers
Regulatory agencies
Quality control laboratories
Procurement agencies
Bioequivalence Quick Contact
Questions on bioequivalence studies or final draft protocols can be sent to:
Dr Matthias Stahl at stahlm@who.int

# Principal Bioequivalence Guideline

- WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability
  - WHO Technical Report Series (TRS) 1003, Annex 6 (2017)
  - Re-published in WHO TRS 1052, Annex 8 (2024) without sections on Biopharmaceutics Classification System (BCS)-based Biowaivers

# Notes on design of bioequivalence studies (NDBS)

- Product specific guidance
- Based on best information available to PQT/MED
  - Revised if more information becomes available
- New guidances being added regularly as EoIs revised or new EoIs are published
  - updated EoIs for HIV/AIDS, influenza-specific antiviral medicines, neglected tropical diseases, and TB
  - new EoI for products for treatment of apnoea in preterm infants
- 129 NDBS guidances currently posted
  - 102 NDBSs posted at this time last year

# NDBS

Most recent additions/updates include advice on the design of studies for:

- Tenofovir alafenamide containing FDCs (HIV EoI)
- Baloxavir marboxil (influenza-specific antivirals EoI)
- Moxidectin (NTD EoI)
- Delamanid, dispersible tablet 25 mg (TB EoI)
- Para-aminosalicylate sodium:  5.52 g powder (for oral solution) in sachet (equivalent to 4 g paminosalicylic acid) (TB EoI)
- Arpraziquantel 150mg and 300mg (scored) dispersible tablet; preferably orodispersible tablet (NTD EoI)
- Lenacapavir tablets and iv solution (HIV EoI)
- Caffeine citrate (apnoea in preterm infants EoI)*

*** New EoI but no NDBS created**

# Lenacapavir

Lenacapavir, tablet, 300 mg

Lenacapavir, solution for subcutaneous injection, 463.5mg/1.5 ml (309mg/ml)

Regarding the solution for injection:

- Aqueous solution for injection
- Unlike cabotegravir long-acting injection (LAI)
  - Suspension for intramuscular injection
  - Cabotegravir LAI requires a BE study
- NDBS for lenacapavir sodium
  - As an aqueous solution, a biowaiver is possible if the proposed product is quantitatively and qualitatively the same in formulation as the comparator product

# ICH M13A

## Bioequivalence for Immediate-release Solid Oral Dosage Forms

- Adopted by ICH on July 23, 2024
- Currently in the process of implementation by numerous national regulatory authorities
- Provides recommendations on conducting bioequivalence (BE) studies during both development and post-approval phases for orally administered immediate-release (IR) solid dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension.
- Will be implemented by PQT/MED on July 1, 2025
- Supersedes portions of current WHO BE guideline (TRS 1052, Annex 8)

# Comparator products

- Lists for comparator products for each treatment area available on PQT/MED website
- All lists updated regularly
  - 12 lists in total
  - Most recently added
    - Treatment of multi-drug resistant bacterial infections
    - Treatment of Apnoea in Preterm infants
- Not all products listed in PQ Expressions of Interest (EOIs) will have comparators indicated on these lists
  - For example, some dispersible products do not have comparable references so conventional product may have to be used as comparator
    - If a comparator is not listed, consult PQT/MED

# Types of biowaivers

- ‘Type of product’-related biowaivers
  - Refer to TRS 1052, Annex 8
- Biopharmaceutics Classification System (BCS)-based biowaivers
  - Refer to ICH Harmonised Guideline M9: Biopharmaceutics Classification System-Based Biowaivers (implemented May 2021)
  - PQT/MED-specific annotations for ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications
  - Biowaiver Application Form: Biopharmaceutics Classification System (BCS)
- Additional strength biowaivers
  - Refer to TRS 1052, Annex 8
  - PQT/MED-specific annotations for Additional Strength Biowaiver Applications
  - PQT/MED Additional Strength Biowaiver application form

# BCS-based biowaivers

## WHO guideline on Biopharmaceutics Classification System-based biowaivers

- Harmonisation of WHO requirements with those of ICH M9 guideline
  - ICH M9 was the foundation for the WHO guideline
- Supersedes the BCS-based biowaiver section of the WHO guidelines on multisource (generic) pharmaceutical products: registration requirements to establish interchangeability
- WHO TRS 1052, Annex 7

# WHO BCS-based biowaivers
# vs.
# ICH M9 BCS-based biowaivers

**Simplification of the definition of 'high solubility' for the purpose of BCS classification of APIs**

- Criterion based on solubility of highest single therapeutic dose
- M9 includes an exception that allows solubility of the highest strength of a product to be considered, based on the linearity of the API's pharmacokinetics, if the API is not highly soluble at highest single dose.

# WHO BCS-based biowaivers vs. ICH M9 BCS-based biowaivers

**Table 1 of the guideline defines allowable differences in excipient content between proposed and comparator products based on percentage differences relative to core weight of the product (%w/w). This is consistent between guidelines.**

- However, in some cases the absolute amount of an excipient present in the GI tract is relevant to whether that excipient will exert an effect on absorption. Differences assessed based on %w/w of core weight may not control for this.
- Therefore, additional criterion introduced to WHO guideline: The total core weight of the proposed product should not deviate by more than 20% from the total core weight of the comparator product.

# BCS-based biowaivers

## WHO guideline on Biopharmaceutics Classification System-based biowaivers

- WHO TRS 1052, Annex 7 (2024)
- PQT/MED will implement this guideline as of January 1, 2025

# Solubility data

BCS-related solubility information is available to guide applicants

- APIs have been identified as eligible for a BCS-based biowaiver application based on information available to PQT/MED
  - Table provided in PQT/MED annotation document
- WHO Biowaiver Project on the ECSPP proposal to waive in vivo bioequivalence requirements for the World Health Organization (WHO) Model List of Essential Medicines
  - Data updated annually
  - See TRS 1052, Annex 6
  - Next update will appear in TRS 1060, Annex 5*

* - Pending endorsement by WHO governing bodies in 2025

# Bioanalysis of study samples

- As a result of the 58th ECSPP meeting held in October 2024
- **Bioanalytical Method Validation and Study Sample Analysis***
  - Harmonisation of WHO requirements with those of ICH M10 guideline
    - ICH M10 was the foundation for the WHO guideline
  - Similar in terms of requirements and recommendations
    - Some additional clarification provided
  - TRS 1060, Annex 6*
  - PQT/MED implemented ICH M10 in May 2023
    - Will transition to the WHO guideline later in 2025

* - Pending endorsement by WHO governing bodies in 2025

# Bioequivalence Trial Information Form (BTIF)

- Must be completed in Word format for every bioequivalence study submitted to PQT/MED
  - Appendix 1 to BTIF also required
- Found on bioequivalence page on PQT/MED website
- A new version of BTIF was posted on January 13. 2023
- Requests:
  - Follow instructions in template
  - Do not change the template

# Safe quality medicines