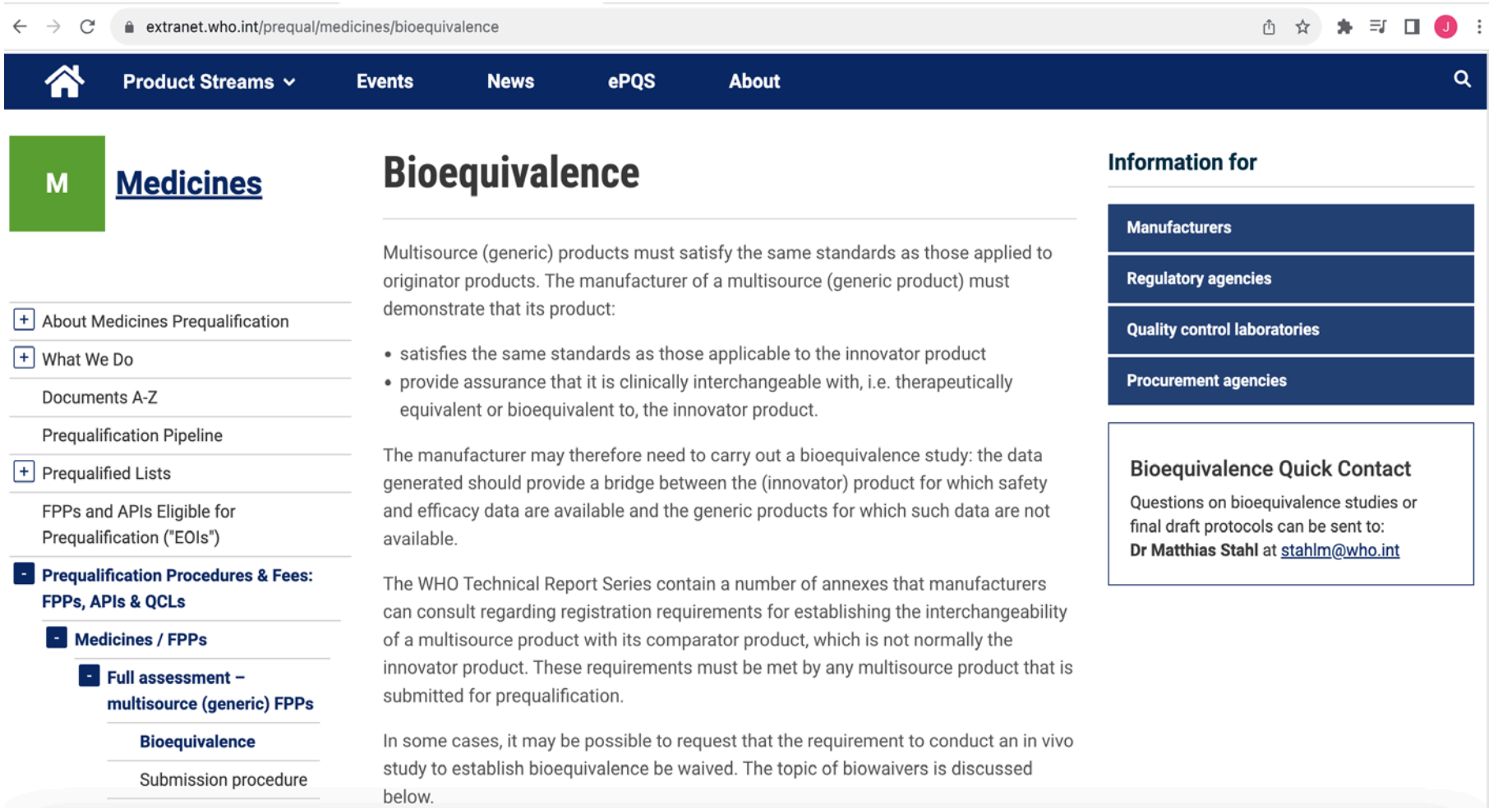
Prequalification Team – Medicines (PQT/MED)

Bioequivalence Assessment Update

Dr. John Gordon
Lead Bioequivalence Assessor

Overview

- Bioequivalence on the PQT/MED website
- 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)


extranet.who.int/prequal/medicines/bioequivalence
Product Streams
Events
News
ePQS
About
M
Medicines
About Medicines Prequalification
What We Do
Documents A-Z
Prequalification Pipeline
Prequalified Lists
FPPs and APIs Eligible for Prequalification ("EOIs")
Prequalification Procedures & Fees: FPPs, APIs & QCLs
Medicines / FPPs
Full assessment – multisource (generic) FPPs
Bioequivalence
Submission procedure
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) 992, Annex 7 (2015)
  - Re-published in WHO TRS 1003, Annex 6 (2017) with additional appendix
    - Appendix 2: Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System (BCS)

extranet.who.int/prequal/medicines/bioequivalence

- Prequalified Lists
- FPPs and APIs Eligible for Prequalification ("EOIs")
- **Prequalification Procedures & Fees: FPPs, APIs & QCLs**
  - **Medicines / FPPs**
    - **Full assessment – multisource (generic) FPPs**
      - **Bioequivalence**
      - Submission procedure
      - API master file (APIMF) procedure
    - SRA-approved multisource (generic) or innovator FPPs
  - Active pharmaceutical ingredients
  - Medicines quality control laboratories
- Post-prequalification Procedures & Fees: APIs, FPPs, QCLs
- Prequalification Reports
- Collaborative Procedures for

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.

GUIDANCE DOCUMENTS

Guidance for organizations performing in vivo bioequivalence studies (revision) (2016)

Guidelines for registration of fixed-dose combination medicinal products (2005)

Guidelines on registration requirements to establish interchangeability (revision) (2017)

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 Update

- As a result of the 57th ECSPP meeting held in October 2023
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability
  - WHO Technical Report Series (TRS) 992, Annex 7 (2015)
  - Re-published in WHO TRS 1003, Annex 6 (2017) with additional appendix
  - To be re-published in WHO TRS 1052, Annex 8*
    - Removal of sections related to BCS-based biowaivers

* - Pending endorsement by WHO governing bodies in 2024

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
  - e.g., updated EoIs for Malaria and RH
  - e.g., new EoI for products for cessation of tobacco use

- 102 guidances currently posted

NDBS

- Most recent additions/updates include advice on the design of studies for:
  - nicotine patches and gum
  - pretomanid
  - tafenoquine
  - glecaprevir/pibrentasvir
  - daclatasvir/sofosbuvir
  - cabotegravir LAI (update)
  - amphotericin B (liposomal) (update)
  - Ledipasvir (update)
  - mebendazole (update)
  - Molnupiravir (update)
  - isoniazid/pyrazinamide/rifampicin (update)
  - isoniazid/rifampicin (update)

GUIDANCE DOCUMENTS

Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQTm (22 November 2018)

Frequent Deficiencies in Bioequivalence Study Protocols

Guidance on bioequivalence studies for reproductive health medicines (25 August 2022)

Guidelines for good clinical practice for trials on pharmaceutical products (TRS850, Annex3, 1995)

Note on paediatric products in PQT Medicines (21 September 2018)

Notes on the design of bioequivalence study: abacavir (14 September 2021)

Notes on the design of bioequivalence study: abacavir/dolutegravir/lamivudine (08 April 2022)

Notes on the design of bioequivalence study: abacavir/lamivudine (11 April 2022)

Notes on the design of bioequivalence study: abacavir/lamivudine/lopinavir/ritonavir (26 July 2021)

Notes on the design of bioequivalence study: albendazole (29 March 2021)

Notes on the design of bioequivalence study: amodiaquine (31 May 2021)

Comparator products

- Lists for comparator products for each treatment area available on PQT/MED website
- All lists updated regularly
  - 10 lists in total
  - Most recently added/revised
    - Treatment of disorders due to use of nicotine (new)
    - Anti-tuberculosis medicines (revised)
- 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 1003, Annex 6
- 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 1003, Annex 6
  - PQT/MED-specific annotations for Additional Strength Biowaiver Applications
  - PQT/MED Additional Strength Biowaiver application form

BCS-based biowaivers update

- As a result of the 57th ECSPP meeting held in October 2023
- **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
  - Will supersede the BCS-based biowaiver section of the WHO guidelines on multisource (generic) pharmaceutical products: registration requirements to establish interchangeability
  - WHO TRS 1052, Annex 7*

* - Pending endorsement by WHO governing bodies in 2024

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.

Bioanalysis of study samples

- ICH Harmonised Guideline M10 *Bioanalytical Method Validation and Study Sample Analysis*
  - Adopted by ICH on 24 May 2022 (Step 4)
  - In process of adoption by national regulatory authorities (NRAs) (Step 5)
    - Swissmedic, CH – May 25, 2022
    - FDA, USA – November 7, 2022
    - Health Canada, Canada – January 20, 2023
    - EC, Europe – January 21, 2023
    - NMPA, China – July 29, 2023

    - Implemented by PQT/MED on May 1, 2023

Bioanalysis of study samples

- WHO is currently developing guidance in the area
- *QAS/23.925 – Bioanalytical Method Validation and Study Sample Analysis*
  - Based on the ICH M10 guideline
  - Currently posted for public comment
    - Based on the ICH M10 guideline
    - See WHO Health Standards and Policy page: Working documents in public consultation
    - Deadline for comments: January 21, 2024

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