Prequalification Team – Medicines (PQTM)

Bioequivalence Assessment Update

Dr. John Gordon
Overview

- Bioequivalence (BE) guideline updates
- Notes on bioequivalence study design
  - Product specific guidance
- Comparator products
- Biowaivers
- Bioequivalence Trial Information Form (BTIF)
- Health verification for study subjects
- Common deficiencies
- BE-related publications from PQT medicines
Principal Bioequivalence Guideline

- WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability
  - Now 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)
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 (TRS) 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)
Guidance for organizations performing in vivo bioequivalence studies

- WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)
  - Updated based on
    - Revision of multisource guideline
    - New guidance on good data management
    - Experience gained in assessment and inspection of bioequivalence studies since 2006
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- Guidelines for registration of fixed-dose combination medicinal products (2005)
- Guidelines on registration requirements to establish interchangeability (revision) (2017)
Guidance update for highly variable APIs

- Bioequivalence guideline (TRS1003, Annex 6)
  - High variability in $C_{\text{max}}$
    - Intra-subject ANOVA-CV of $\geq 30\%$
    - “Reference-scaled average bioequivalence”
  - Estimation of variability based on replicate administration of comparator product
  - Widening of acceptance criteria for $C_{\text{max}}$ based on estimated variability
    - “scaled” acceptance criteria
Guidance update for highly variable APIs

- Guidance note posted to PQTm website in June 2017
- “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQTm”
  - evidence to suggest that very high variability may be observed with the AUC parameter for a limited number of APIs
  - there may be situations where the scaling of the acceptance criteria for AUC in bioequivalence studies conducted with these APIs may be justified without an undue increase in risk regarding therapeutic safety and efficacy of the proposed drug product.
On a trial basis, PQTm will consider scientific justifications from applicants to permit the scaling of the AUC acceptance criteria for data from full replicate design bioequivalence studies.

The applicant should receive confirmation that PQTm will accept reference-scaled bioequivalence for AUC for the specific API under consideration, as described in Section 7.9.3 of TRS1003, Annex 6, prior to undertaking the bioequivalence study. In cases where reference-scaling for the AUC acceptance limits is accepted, a four period, full replicate design study should be conducted to demonstrate bioequivalence, in order to assess the variability associated with each product.
Guidance update for highly variable APIs

- The following requirements apply:
  - A request to apply the scaling approach described in Section 7.9.3 to AUC data should be submitted to PQTm along with a final draft of the proposed study protocol prior to undertaking the study.
  - The request should report the data available from literature or pilot data demonstrating the magnitude of the variability in the AUC parameter. It should also include a scientific discussion of the possible impact of widened AUC acceptance limits on the therapeutic/clinical effect and safety of the API and drug product under development.
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**GUIDANCE DOCUMENTS**

**Design of bioequivalence studies**

The WHO Prequalification Team: medicines (PQTM) supports applicants in addressing specific scientific issues related to product development and design of bioequivalence studies that are intended to support an application for prequalification. It strongly recommends that applicants submit the final draft of their bioequivalence study protocol for review before embarking on the study. Questions on bioequivalence studies or final draft protocols can be sent to the head of medicines assessments.

Support from PQTM is also available in the form of WHO medicines prequalification guidance on the design of bioequivalence studies in the following therapeutic areas for the products indicated:

- hepatitis: daclatasvir, entecavir, simprevir, sofosbuvir, sofosbuvir/ledipasvir, tenofovir
- HIV: atazanavir/ritonavir, darunavir, darunavir/ritonavir, dolutegravir, efavirenz, emtricitabine/tenofovir/dolutegravir, lamivudine/tenofovir/dolutegravir, tenofovir
- malaria: artemether/lumefantrine, dihydroartemisinin/piperaquine
- neglected tropical diseases: albendazole, diethylcarbamazine, ivermectin, mebendazole, praziquantel
- tuberculosis: clofazimine, cycloserine, terizidone.

A guidance document on bioequivalence studies for reproductive health medicines is also available.

**GUIDANCE DOCUMENTS**

- Guidelines for good clinical practice for trials on pharmaceutical products (1995)
- Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQTM (09 June 2017)
Notes on bioequivalence study design

- Product specific guidance
- Based on best information available to PQTm
  - Maybe revised if more information becomes available
- New guidances being added regularly
  - Anticipate >10 new documents will be added in coming months
  - Most recent additions include advice on the design of studies for:
    - Darunavir + ritonavir
    - Miltefosine
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- HIV: atazanavir/ritonavir, darunavir, darunavir/ritonavir, dolutegravir, efavirenz, emtricitabine/tenofovir/dolutegravir, lamivudine/tenofovir/dolutegravir, tenofovir
- malaria: artemether/lumefantrine, dihydroartemisinin/piperaquine
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Guidance Documents

- Guidelines for good clinical practice for trials on pharmaceutical products (1995)
- Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQTm (09 June 2017)
- Guidance on bioequivalence studies for reproductive health medicines (7 July 2014)
- Notes on the design of bioequivalence study: albendazole (13 September 2015)
- Notes on the design of bioequivalence study: artemether + lumefantrine (1 April 2008)
- Notes on the design of bioequivalence study: atazanavir + ritonavir (1 April 2008)
- Notes on the design of bioequivalence study: clofazimine (18 November 2016)
- Notes on the design of bioequivalence study: cycloserine (13 October 2015)
Comparator products

- Lists for comparator products for each treatment area available on PQTm website
- All lists updated in August/September 2017 period
- 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 PQTm
Comparator products: Where can they be purchased?

- International Council for Harmonization (ICH)
  - formerly International Conference on Harmonization
  - Inaugural Assembly meetings for new association took place on 23 October 2015
  - Evolution of mission and objectives

- Comparator lists indicate that: “Comparator products should be purchased from a well-regulated market with a stringent regulatory authority.”
Comparator products: Where can they be purchased?

- A regulatory authority that is
  - a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
  - an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
  - a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.
Comparator Products

If WHO comparator product cannot be located in those markets, consult PQTm

- Identification of alternate markets for sourcing particular products
- Assistance identifying pharmaceutical distributors

If a comparator is not indicated on our PQTm list then contact PQTm
Biowaivers

- *In vitro* approaches for demonstrating safety and efficacy of products *in lieu* of conducting *in vivo* bioequivalence studies

- Biopharmaceutics Classification System (BCS) – based biowaivers
  - Suitable for products containing eligible APIs
  - Abbreviated submission if API is on the eligibility list

- Additional strengths biowaivers
  - Suitable for additional strengths in a product line when one of the strengths has shown *in vivo* bioequivalence to the comparator
BCS-based Biowaivers eligible APIs

Medicines for HIV/AIDS and related diseases
- Abacavir sulfate (Class III)
- Emtricitabine (Class I)
- Fluconazole Polymorphs II & III (Class I)
- Lamivudine (Class III)
- Stavudine (Class I)
- Zidovudine (Class I)

Neglected Tropical Disease medicines
- Diethylcarbamazine (Class III)*

Anti-tuberculosis medicines
- Ethambutol (Class III)
- Isoniazid (Class III)
- Levofloxacin (Class I)
- Linezolid (Class I)
- Moxifloxacin HCl (Class I)
- Ofloxacin (Class I)
- Pyrazinamide (Class III)

Joint UNICEF, UNFPA & WHO MEETING with manufacturers and suppliers
BCS-based Biowaivers

- Do not use classifications provided in 2006 WHO TRS 937, Annex 8

- ECSPP overseeing the development of a new biowaiver classification list
  - Living document

- Information on equilibrium solubility experiments
  - Appendix 2 of WHO TRS 1003, Annex 6 (2017)
  - Document with more technical detail under development by ECSPP
Bioequivalence Trial Information Form (BTIF)

- Must be completed in Word format for every bioequivalence study submitted to PQTm
- New version of BTIF posted in January 2017
  - Clarification of some wording
  - Rearrangement of some sections
- Further revised version coming soon
  - Will include two electronic appendices
    - Individual pharmacokinetic results (AUC and Cmax) for each subject
    - Individual concentration data for each subject
Health verification for subjects

- Good Clinical Practices (GCP) require that the rights, safety, and well-being of trial subjects be given top priority in every trial conducted.
- Subjects should be recruited into the study only if their health is fully verified
  - Including verification that serum biochemistry and haematology parameter values are within pre-defined normal acceptance ranges
  - Do not engage in subjective practices with respect to haematology
Common deficiencies - BTIF

- Summaries should be included where requested, not just a reference to a location in the study report.
- On the other hand, just summaries when requested, not pages and pages of raw data.
- State the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in section 3.4.3.1 under point b), indicate in which Annex (number) the Certificate of Analysis can be found.
- Ensure that the electronic submission has the same file/naming structure as the one employed to state the location of the documents and to include annexes of the BTIF as separate files.
Common deficiencies - Documentation

- Electronic files in Module 5 not given meaningful names
  - Should be e.g., Section 16.1.1 – 16.2.5
  - Not Volume 1 of 17, Vol. 2 of 17, etc.

- PDF documents not in text selectable format
  - Should be in text selectable format for ease of assessment
Common deficiencies

- Comparator documentation not complete
  - Proof of purchase
  - Proof of shipment
  - Proof of storage conditions
    - From time of purchase to time of study
- Application forms only submitted in PDF format
  - *In vivo* bioequivalence study
    - Bioequivalence Trial Information Form (BTIF)
  - BCS-based biowaiver
    - Biowaiver Application Form: Biopharmaceutics Classification System (BCS)
- Additional strengths biowaiver
  - Biowaiver Application Form: Additional strengths

Joint UNICEF, UNFPA & WHO MEETING with manufacturers and suppliers
Common deficiencies

- Comparative dissolution information
  - Selection of sampling times e.g., include 15 min
  - Sample filtration not defined and/or not during sample collection
    - Filter with inline filter or filter on the end of the sampling probe
- Characterization of biobatch
  - Collect every piece of information you can think of!
  - Dissolution studies in multiple media including release media
- Dissolution study protocol
  - Should be created before dissolution study is conducted
  - Should be used for all studies for which data will be compared
BE-related publications from PQT medicines

- PQTm encouraged to interact with stakeholders and scientific community
- Interaction occurs through various pathways
  - Publication of information on WHO PQ website
  - Participation in assessment training sessions
  - Participation in scientific meetings
  - Publication in peer-reviewed scientific literature

- PQTm BE assessment team active in contributing via publications
  - PQ-specific themes
  - Scientific community in general
Statistical approaches to indirectly compare bioequivalence between generics: a comparison of methodologies employing artemether/lumefantrine 20/120 mg tablets as prequalified by WHO

Luther Gwaza · John Gordon · Jan Welink · Henrike Potthast · Henrik Hansson · Matthias Stahl · Alfredo García-Arieta

Abstract
Purpose The objective of this study was to compare different methods of adjusted indirect comparisons that can be used to investigate the relative bioavailability of different generic products. To achieve this goal, generic artemether/lumefantrine 20/120 mg tablets that have been prequalified by the World Health Organization (WHO) were selected as model products for study.

Methods Data from three bioequivalence studies conducted independently that compared three generics with the same reference product were used to indirectly determine the relative bioavailability between the generics themselves.

Results The different methods of indirect comparison examined in this study provide consistent results. Methods based on the assumption of a large sample size give slightly
Previously:

Adjusted Indirect Treatment Comparison of the Bioavailability of WHO-Prequalified First-Line Generic Antituberculosis Medicines

L Gwaza\textsuperscript{1,2}, J Gordon\textsuperscript{3}, J Welink\textsuperscript{4}, H Potthast\textsuperscript{5}, H Leufkens\textsuperscript{1,4}, M Stahl\textsuperscript{6} and A García-Arieta\textsuperscript{7}

Approval of generic medicines is based on bioequivalence with the innovator product, but it is not unusual for generics to be interchanged with each other. This study investigated the differences in bioavailability between World Health Organization–prequalified antituberculosis generics by means of indirect comparisons to ensure interchangeability between these diverse generics. Data on 22 products containing isoniazid, rifampicin, pyrazinamide, or ethambutol in single- or fixed-dose combination were included. The indirect comparison between generics shows that the differences, expressed as 90\% confidence intervals, are always less than 30\%. Furthermore, assurances regarding interchangeability of two generic products are reduced when either the point estimate ratios in the original studies are shifted from unity by more than 5\% or when the width of the 90\% confidence interval is large. From a bioequivalence perspective, not only are the generics bioequivalent with the reference but also all these generics can be interchanged without safety/efficacy concerns.

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\textit{CLINICAL PHARMACOLOGY & THERAPEUTICS}
Influence of point estimates and study power of bioequivalence studies on establishing bioequivalence between generics by adjusted indirect comparisons

Luther Gwaza\textsuperscript{1,2} · John Gordon\textsuperscript{3} · Henrike Potthast\textsuperscript{4} · Jan Welink\textsuperscript{5} · Hubert Leufkens\textsuperscript{1} · Matthias Stahl\textsuperscript{6} · Alfredo García-Arieta\textsuperscript{7}

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Abstract

\textit{Purpose} Adjusted indirect comparisons can be used to investigate bioequivalence between generic products that are bioequivalent with a common reference product. In previous

\textit{Results} The indirect comparisons could conclude equivalence between generics only when (a) point estimate differences between generics were low (≤5.5 \%) for any sufficiently powered study (>80 \%), or (b) the differences were large
Original article

Interchangeability between first-line generic antiretroviral products prequalified by WHO using adjusted indirect comparisons

Luther Gwaza\textsuperscript{1,2}, John Gordon\textsuperscript{3}, Jan Welink\textsuperscript{4}, Henrike Potthast\textsuperscript{5}, Hubert Leufkens\textsuperscript{1,4}, Matthias Stahl\textsuperscript{6}, Alfredo García-Arieta\textsuperscript{7*}

Background: The scaling-up of access to antiretroviral therapy, particularly in low- to middle-income countries, was facilitated by the introduction and widespread use of generic antiretroviral medicines and fixed-dose combinations. Generic medicines are approved by regulatory authorities based on the demonstration of bioequivalence. When studies are conducted in different settings, the resulting bioequivalence comparisons may vary, which is important to account for. Adjusted indirect comparisons was calculated using the homoscedastic method that uses the conventional $t$-test, and assumes homogeneity of variances between the studies and small sample sizes. The combined standard deviation of both bioequivalence studies was calculated from the variability of each individual study.
Assessment of the interchangeability between generics

Luther Gwaza¹,², BPharm, MPhil; John Gordon³, PhD; Henrike Potthast⁴, PhD; Marc Maliepaard⁵, PhD; Jan Welink⁵, Hubert Leufkens¹-⁵, PhD; Matthias Stahl⁶, MD; Alfredo García-Arieta⁷, PhD

Generic medicines are approved by regulatory authorities based on demonstration of bioequivalence with the innovator, however, direct comparison between all available generics of the same innovator to ensure interchangeability between them is not feasible. With

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Commentary

Global Harmonization of Comparator Products for Bioequivalence Studies

Luther Gwaza,1,2 John Gordon,3 Hubert Leufkens,1 Matthias Stahl,4 and Alfredo García-Arieta5,6

Received 8 November 2016; accepted 24 February 2017

Abstract. Comparator products should be the products that were shown to be safe and efficacious in pivotal clinical trials to ensure prescribability of generics. The use of a common comparator ensures switchability between generics. The selection of the comparator is a national responsibility and may be different between countries. This paper discusses the current recommendations on selection of comparators, the associated problems, and the possibility of harmonization. Most countries follow the World Health Organization (WHO) recommendations for selecting comparator products and require the comparator product to be obtained from their national markets to ensure switchability between the local comparator and their generics. These recommendations are only feasible in the few countries where the
Contributions to books discussing international approaches to BE-related topics


Safe quality medicines