Prequalification Team – Medicines (PQT/MED)

Bioequivalence Assessment Update

Dr. John Gordon
Overview

- Bioequivalence (BE) on the PQT/MED website
- WHO – PQT/MED BE guidance
- Notes on bioequivalence study design
  - Product specific guidance
- Review of study protocols
  - Deficiencies observed in study protocols
- Comparator products
- Biowaivers
  - f2 calculation
- COVID medicines
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.
Guidance for designing BE studies

• General WHO guidelines published in Technical Report Series (TRS)
  • WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)

• PQT/MED-specific guidance found on PQ website

https://extranet.who.int/pqweb/medicines
Guidance

“Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability".

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**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)

**Design of bioequivalence studies**

WHO supports applicants in addressing specific scientific issues related to product
Notes on the Design of Bioequivalence Study (NDBS)

- Product specific guidance individualized for each API or combination of APIs included in the Expressions of Interest (EoI)

- Based on best information available to PQT/MED
  - Updated as more information becomes available to PQT/MED

- 71 guidances + RH guidance currently posted

- Always check for most up-to-date version on NDBS when planning a BE study
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 (11 March 2021)

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 (03 July 2019)

Notes on the design of bioequivalence study: abacavir/lamivudine (29 March 2021)

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)
Applicants planning to conduct bioequivalence (BE) studies for submission to PQT/MED should submit a final draft of the study protocol to PQT/MED for comment prior to undertaking the study.

Purpose:
- Assist applicants develop studies that will best be able to detect differences in *in vivo* performance between drug products.
- Minimise factors that could introduce variability into the study data.
- Align with PQT/MED guidelines and requirements.

Frequent deficiencies in protocols.
A guidance document on bioequivalence studies for reproductive health medicines is also available.

**GUIDANCE DOCUMENTS**

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- Notes on the design of bioequivalence study: amodiaquine (09 March 2018)
Comparator products

- Lists for comparator products for each treatment area available on PQT/MED website
- All lists updated regularly
  - 9 lists currently available

- 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
Recommended comparator products:
Therapeutics against COVID-19

Comparator products should be purchased from a well-regulated market with stringent regulatory authority.¹

<table>
<thead>
<tr>
<th>Invited medicinal products (refer to EOI for more information e.g., requirements for scoring)</th>
<th>Recommended comparator product (Strength, Manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baricitinib 2 mg tablet</td>
<td>Oluminant (2 mg tablet, Eli Lilly and Co)</td>
</tr>
<tr>
<td>Dexamethasone tablet, 1.5 mg, 2 mg and 6 mg (dexamethasone as base)</td>
<td>Dexamethasone 1.5 mg, 2 mg and 6 mg tablet (dexamethasone as base), Hikma Pharmaceuticals USA Inc.²</td>
</tr>
<tr>
<td>Dexamethasone oral solution, 2 mg/5 ml and 10 mg/5 ml (dexamethasone as base or as sodium phosphate)</td>
<td>ForteCortin 0.5, 1.5, 2, 4 and 8 mg tablets (dexamethasone as base), Merck</td>
</tr>
<tr>
<td>Dexamethasone solution for injection, containing dexamethasone base 3.3 mg/ml or 6.6 mg/ml, as sodium phosphate (equivalent to dexamethasone phosphate 4 mg/ml or 8 mg/mg)</td>
<td>Martapan oral solution (2 mg/5 ml dexamethasone as sodium phosphate), Martindale Pharma</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone sodium phosphate, solution for injection eq. 4 mg/ml and 10 mg/ml, Fresenius Kabi USA LLC²</td>
</tr>
<tr>
<td></td>
<td>ForteCortin 4 and 8 mg/ml (as sodium phosphate)</td>
</tr>
</tbody>
</table>
Types of biowaivers

• ‘Type of product’-related biowaivers
  • Refer to TRS 1003, Annex 7

• Biopharmaceutics Classification System (BCS)-based biowaivers
  • Refer to ICH Harmonised Guideline M9: Biopharmaceutics Classification System-Based Biowaivers
  • 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 7
  • PQT/MED-specific annotations for Additional Strength Biowaiver Applications
  • PQT/MED Additional Strength Biowaiver application form
For a biowaiver, comparative dissolution between Test and Comparator is often needed to show similarity

- If both products dissolve ≥85% in 15 min then considered similar
- If not, then a similarity calculation is required: f2

There are rules for the calculation of f2 that must be followed

- Minimum of three (3) timepoints (zero excluded!)
- Timepoints should be the same for both products
- Mean values should be employed for each timepoint
- Not more than one mean value of ≥85% dissolved for either of the products
- Variability in mean data must be considered (next slide)
Variability in mean data for f2

- For a BCS-based biowaiver, %RSD for a mean data point should not be more than 20% at early time-points (up to 10 minutes) and should not be more than 10% at other time points.

- For an additional strength biowaiver, the same %RSD requirements should be employed if dissolution is complete in 45 min or less.

- If dissolution is complete only after 45 min, then %RSD at 15 minutes should be ≤ 20% and ≤ 10% for later timepoints.

- Variability in excess of the above challenges the validity of the f2 calculation and those data points should be excluded from calculations (discuss with PQT/MED).
The PQ-invited small molecule medicines for COVID-19 disease

Dexamethasone
1. **Dexamethasone tablet**, containing dexamethasone base 1.5mg, 2mg, 6mg
2. **Dexamethasone oral solution**, containing dexamethasone base 2mg/5ml or 10mg/5ml, as the base or sodium phosphate
3. **Dexamethasone solution for injection**, containing dexamethasone base 3.3mg/ml or 6.6mg/ml*, as the sodium phosphate
   (*equivalent to dexamethasone phosphate 4mg/ml or 8mg/ml, respectively)

Janus Kinase Inhibitors
Baricitinib 2 mg tablets

Direct-Acting Antivirals
Molnupiravir 200 mg capsules
Nirmatrelvir 150 mg tablets (x2) + ritonavir 100 mg tablet co-pack
Dexamethasone products

- **Notes on the Design of Bioequivalence Study: Dexamethasone**

- Three types of product invited
  - Oral tablets
  - Oral solution
  - Solution for injection
Dexamethasone tablets

- Recommendations for design of BE study in NDBS
  - BE study should employ highest strength
  - Additional strength BW possible for lower strengths
    - Proportionality of formulations
    - Similarity of dissolution profiles

- BCS-based biowaiver may be possible
  - Details described on p.3 of NDBS
Dexamethasone oral solution

• Recommendations for design of BE study in NDBS
  • BE study should employ 6 mg dose
  • Additional strength BW possible for other strength
    • Proportionality of formulations

• ‘Type of product’ biowaiver may be possible
  • Oral solution can qualify for a biowaiver if formulation is Q&Q with comparator product formulation
  • Details described on p.2-3 of NDBS
Dexamethasone solution for injection

- ‘Type of product’ biowaiver may be possible
  - Oral solution can qualify for a biowaiver if formulation is Q&Q with comparator product formulation
  - Details described on p.2 of NDBS
- Differences in excipients could result in additional clinical data requirements
Baricitinib products

• **Notes on the Design of Bioequivalence Study: Baricitinib**

• Recommendations for design of BE study in NDBS

• BCS-based biowaiver may be possible
  • Details described on p.2 of NDBS
  • API may be BCS Class III – data needed to confirm
Molnupiravir products

- Notes on the Design of Bioequivalence Study: Molnupiravir

- Recommendations for design of BE study in NDBS

- BCS-based biowaiver may be possible
  - Details described on p.2 of NDBS
  - API appears to be highly soluble
  - Permeability / site of biotransformation unclear
    - M9-compliant data needed
Nirmatrelvir + Ritonavir co-pack products

• Notes on the Design of Bioequivalence Study: Nirmatrelvir + Ritonavir

• Recommendations for design of BE study in NDBS

• The product is a co-pack so, if applicant has a ritonavir product already prequalified, a study with only the nirmatrelvir component may be possible

• BCS-based biowaiver may be possible
  • Solubility/permeability data required