Bioequivalence Testing within the Prequalification Programme

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UN Prequalification Programme for Priority Essential Medicines

Action plan of UN from 2001 for expanding access to selected priority medicines

Objective:

To ensure quality, efficacy and safety of medicines procured using international funds (e.g. GFATM, UNITAID)

Components:

● Evaluation of Quality, Safety and Efficacy of prioritized essential medicines, inspections of manufacturers and monitoring of the products after their prequalification.

● Prequalification of quality control laboratories.

● Building capacity of regulators, manufacturers and quality control laboratories.
Categories of medicines invited

- Primary categories of medicines:
  - HIV/AIDS
  - Malaria
  - Tuberculosis

- Later added:
  - Reproductive health
  - Influenza
  - Acute diarrhoea

- Potentially other categories of products, if there is the need
Essential steps of PQ evaluation procedure

- Limited to priority essential medicines
- Need is specified and agreed upon by WHO treatment programmes
- Invitation for Expression of Interest (EOI) is published
- Interested parties submit dossiers
- Dossiers receive initial screening
- Full dossiers are assessed
- Inspections are conducted at manufacturing sites and at CROs
- Samples are tested, if needed
- If outcome is positive, pharmaceutical product is listed on the website, including product information (SPC, PIL), assessment report (WHOPAR) and inspection report (WHOPIR)
Two prequalification routes

Invitation for expression of Interest

Medicine not assessed by SRA
- Dossier and SMF submitted for assessment
- WHO assessment and inspections organized
- Compliance

Prequalification

Medicine assessed by SRA
- Valid for innovators and generics
- SRA registration (assessment and compliance check)
- Simplified review
- Acceptance
Prequalification assessment

● Multisource products not registered by SRA

  – **Assessment**
  
  – **Quality:** information on starting materials and finished product, (API details, specifications, stability data, formulation, manufacturing method, packaging, labelling etc.)
  
  – **Interchangeability with reference product** (efficacy and safety): Report of bioequivalence, biowaiver or clinical study demonstrating interchangeability with reference product
  
  – ** Inspection** of manufacturers and CROs
  
  – **Laboratory analysis** in case of need
  
  – **Monitoring** after prequalification
Evaluation procedure

Assessment of product dossiers

- (Quality specifications, pharmaceutical development, production, control, stability, bioequivalence, etc).
- **Teams of professionals from national Drug Regulatory Authorities (DRA): Including Brazil, China, Canada, Denmark, Estonia, Finland, France, Germany, Hungary, Indonesia, Malaysia, Philippines, Spain, South Africa, Sweden, Switzerland, Tanzania, Uganda, UK, Zimbabwe ...**

**Copenhagen assessment week**

- 8 to 30 assessors together during one week at least every two months at UNICEF in Denmark
- Every dossier is assessed by at least four assessors.
- An assessment report is issued - signed by assessors
- Letter summarizing the findings and asking for clarification and additional data if necessary is sent first by e-mail to the applicant followed by surface mail
Establishing Bioequivalence

- Comparative pharmacokinetic studies
  - *In vivo* comparative bioavailability studies
  - Comparison of performance of products based rate and extent of absorption of drug substance from each formulation
    - Area under the concentration-time curve (AUC)
    - Maximal concentration (Cmax)
    - Time to maximal concentration (Tmax)

- Comparative pharmacodynamic studies

- Comparative clinical trials

- Comparative *in vitro* methods
  - Biopharmaceutics Classification System (BCS)-based biowaivers
Comparator (Reference) Products

- A pharmaceutical product with which the multi-source product is intended to be interchangeable in clinical practice

- The selection of the comparator product is usually made at the national level by the drug regulatory authority

- A different set of circumstances apply to comparator selection for Prequalification Programme (PQP)
Comparator (Reference) Products

Example of how a national RA can select a comparator:

- choose national granted innovator for which quality, safety and efficacy has been established (nationally authorised innovator)
- choose WHO comparator product from the comparator list (WHO comparator product)
- choose innovator product from well-regulated country (ICH et al. innovator)
- if no innovator comparator is available, a generic market leader can be chosen
Comparator (Reference) Products

Selection of a comparator for a single national market:

- Difficult to translate when other countries are at stake
- National comparator may be the national market leader

No problem in that market but others!?
EMA (Europe)

Differentiate between use for single market or many countries!

EMA:

Austria  France  Latvia  Poland
Belgium  Germany  Liechtenstein  Portugal
Cyprus  Greece  Lithuania  Slovak Republic
Czech Republic  Hungary  Luxemburg  Slovenia
Denmark  Iceland  Malta  Spain
Estonia  Ireland  The Netherlands  Sweden
Finland  Italy  Norway  United Kingdom

For an abridged application claiming essential similarity to a reference product, application to numerous Member States based on bioequivalence with a reference product from one Member State can be made.
Prequalification program
Comparator (Reference) Products

- Comparator products should be obtained from a well regulated market with stringent regulatory authority i.e., from countries participating in the International Conference on Harmonization (ICH).

- Countries officially participating in ICH:
  - ICH members: European Union, Japan and USA
  - ICH observers: Canada and EFTA as represented by Switzerland
  - Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.
Comparator lists

- List of acceptable comparator products for each treatment area on WHO PQP website
  
  [http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_comparator.htm](http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_comparator.htm)

- There are instances when a comparator is not available in the ICH region
  
  - e.g., Terizidone 300mg
    
    - Terivalidin 250 mg (Sanofi-Aventis, South Africa)
  
  - e.g., Artesunate + Amodiaquine 100 mg + 270 mg FDC
    
    - Coarsucam (Sanofi-Aventis)
# Recommended comparator products: anti-tuberculosis medicines

<table>
<thead>
<tr>
<th>Invited medicinal products</th>
<th>Recommended comparator product (Strength, Manufacturer)</th>
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<tbody>
<tr>
<td><strong>Single ingredient first-line anti-tuberculosis medicines</strong></td>
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</tr>
<tr>
<td>Ethambutol, 100 mg tablet and 200 mg, 275 mg and 400 mg tablet/capsule, 25 mg/ml oral solution</td>
<td>Myambutol (400 mg tablet, Riemser Arzneimittel or Teofarma) Ethambutol hydrochloride (100, 400 mg tablet, West Ward, US²)</td>
</tr>
<tr>
<td>Isoniazid, 50 mg, 100 mg and 150 mg tablet and 300 mg tablet/capsule</td>
<td>Isozid (100 mg tablet, Fatol) Isoniazid (100 mg, 300 mg tablet, Sandoz, US²)</td>
</tr>
<tr>
<td>Pyrazinamide, 150 mg tablet and 250 mg and 400 mg tablet/capsule, 30 mg/ml oral syrup</td>
<td>Pyrazinamide Lederle (500 mg tablet, Riemser Arzneimittel) Pyrazinamide (500 mg tablet, Dava Pharm Inc, US²)</td>
</tr>
<tr>
<td>Rifampicin, 150 mg and 300 mg capsule</td>
<td>Rimactane (150 mg, 300 mg tablet, Novartis or Sandoz) Rifadin (150 mg, 300 mg capsule, Sanofi-Aventis) Rifampicin (150mg, 300 mg, Sandoz, NL)</td>
</tr>
<tr>
<td>Streptomycin, 0.75 g and 1 g powder for solution for injection (vial)</td>
<td>Streptomycin (1g/2.5ml injection, Pfizer, US²)</td>
</tr>
<tr>
<td><strong>Fixed-dose combination products of first-line anti-tuberculosis medicines:</strong></td>
<td></td>
</tr>
<tr>
<td>Isoniazid + Rifampicin, 75 mg + 150mg, 150 mg + 150 mg and 150 mg + 300 mg tablet/capsule</td>
<td>Rifenah (rifampicin 300 mg + isoniazid 150 mg tablet, Sanofi-Aventis), Rifamate (rifampicin 300 mg + isoniazid 150 mg capsule, Sanofi-Aventis, US²)</td>
</tr>
</tbody>
</table>

For other invited fixed-dose combination products of anti-tuberculosis medicines, use appropriate combination of the recommended single ingredient comparator products.
Comparator (Reference) Products

**Information Requirements**

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme.
Establishing Bioequivalence

- Comparative pharmacokinetic studies
  - *In vivo* comparative bioavailability studies
  - Comparison of performance of products based on rate and extent of absorption of drug substance from each formulation
    - Area under the concentration-time curve (AUC)
    - Maximal concentration (Cmax)
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- Comparative pharmacodynamic studies

- Comparative clinical trials

- Comparative *in vitro* methods
  - Biopharmaceutics Classification System (BCS)-based biowaivers
Typical *in vivo* BE Design

- Single-dose administration
- Cross-over (within-subject) comparison
- Healthy volunteers
- Administration with or without food
  - Fasted study is the norm
- Thoroughly validated bioanalytical method
- Data from parent compound used for BE decision
- Analysis should be carried out on the logarithmically transformed $AUC_T$ and $C_{max}$ data
Acceptance criteria

- Single-dose, two-way crossover study
- Average bioequivalence
- AUC: 90% Confidence Interval (CI) within 80.0-125.0%
- Cmax: 90% CI within 80.0-125.0%
Alternative *in vivo* BE Study Designs

- **Single-dose administration**
- **Multiple-dose administration**
  - Patient-only studies
  - Possibly for MR product
Alternative *in vivo* BE Study Designs

- **Crossover Design**
  - Each subject administered both test and comparator
  - Within-subject comparison
  - Preferred

- **Parallel Design**
  - Each subject administered test or comparator
  - Between-subject comparison
  - Only recommended for extremely long half-life drugs
  - Consult WHO
    - e.g., medroxyprogesterone acetate depot injection
Crossover Design

- Blood samples are collected and assayed
  - Before and several times after drug administration. No need after 72 h
- Prior to period 2, pre-dose levels must be <5% of Cmax of 2nd period
- Wash out period must take into account the slow metabolizers
- Minimum wash out: 7 days (1 week)
Drugs with long elimination $t_{1/2}$: Parallel

- Normally wash-out period should not exceed 3-4 weeks
- If a larger wash-out period is necessary a parallel design may be more appropriate
- Variability will be larger, needs higher sample size
  - Parallel design: Total variability (intra+inter)
  - Cross-over: Intra-subject variability
- Sampling: Up to 72 h
Alternative *in vivo* BE Study Designs

- **Unknown variability**
  - Estimates of intra-subject CV not available
  - Pilot Study
  - Two-stage group sequential two-way crossover design
    - Details of statistical plan in protocol
    - Overall Type 1 error must be preserved
      - Adjusted level of significance resulting in CIs higher than 90%

- **High variability in Cmax**
  - Intra-subject ANOVA-CV of ≥ 30%
  - Replicate design
    - Widening of acceptance criteria for Cmax based on estimated variability
In vivo BE Study Design

- Administration of products under fasted or fed conditions?

- Fasted conditions
  - Study conducted under fasted conditions the norm
  - Comparator product labeling (SPC)
    - Specifies fasted conditions
    - Does not specify fasted/fed for administration
    - States that either fasted or fed administration

- Fed conditions
  - If specified in comparator product labeling (SPC)
In vivo BE Study Design

Administration of products under fasted or fed conditions?

Fed conditions
- If specified in comparator product labeling (SPC)
- Type of meal to be consumed
  - high-fat, high-calorie meal
  - “standard” or typical breakfast

Administration under both fasted and fed conditions
- Not generally necessary for immediate-release products
- Required for modified-release products
Examples
HIV/AIDS Medicines

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - Lamivudine
    - Administration with respect to (wrt) food not specified
    - Fasted
  - Stavudine
    - Maybe taken with or without food
    - Fasted
  - Zidovudine
    - Administration with respect to (wrt) food not specified
    - Fasted
  - Note: as monocomponent products: BCS-based biowaiver
Examples
HIV/AIDS Medicines

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - Didanosine (enteric-coated)
    - Delayed-release formulation
    - Two studies required: Fasted and fed conditions
  - Tenofovir disoproxil fumarate
    - US labeling of comparator: “The dose is one 300 mg tablet once daily taken orally, without regard to food.”
    - European labeling of comparator: “…(one tablet) once daily taken orally with food.”
    - Either accepted
Establishing bioequivalence

Different approaches for establishing equivalence

- Standard: in vivo BE studies
- PD studies
- Clinical studies
- In vitro methods
BCS-based Biowaiver guidance


Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms


BCS-based Biowaiver

- Eligibility for BCS-based Biowaiver
  - General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications

- Requirements for BCS-based Biowaiver
  - General Notes on BCS-based Biowaiver Applications
  - Biowaiver Application Form: Biopharmaceutics Classification System (BCS)

- http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_implementation.htm
Biopharmaceutics Classification System

- Biopharmaceutics Classification System (BCS)
  - Classification system for drug substances
    - Aqueous solubility
    - Intestinal permeability

- Drug substance classification according to BCS

<table>
<thead>
<tr>
<th>BCS Classification</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS class I</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>BCS class II</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>BCS class III</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>BCS class IV</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>
Current Situation

- Programme has reviewed existing information on the solubility, bioavailability, and dissolution data of the invited medicines

- The following drug substances have been identified as eligible for a BCS-based biowaiver application as either monocomponent or fixed-dose combination (FDC) products

- Monocomponent or FDC products containing other drug substances must be supported with in vivo BE data
Current Situation

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

- Anti-tuberculosis medicines
  - Ethambutol (Class III)
  - Isoniazid (Class III)
  - Levofloxacin (Class I)
  - Ofloxacin (Class I)
  - Pyrazinamide (Class III)
Biowaiver assessment

- Drug substance classification
  - Solubility
  - Permeability / absorption

- Risk assessment

- Drug product
  - Excipient comparison
  - Comparative *in vitro* dissolution
Class I Drug Substances

- Selection of comparator product
  - As discussed earlier

- Biobatch reflective of proposed commercial product

- Comparison of products
  - Should employ well known excipients in usual amounts
  - Beneficial to contain similar amounts of the same excipients
  - Critical excipients (e.g., mannitol, sorbitol, surfactants), if present, should not differ qualitatively or quantitatively
Class I Drug Substances

- Comparative *in vitro* dissolution
  - Comparative testing should ensure the similarity of the test and comparator product in three different pH media considered relevant for absorption from the GI tract
  - Comparative *in vitro* dissolution testing should be conducted in at least three media of pH 1.2, 4.5, and 6.8
    - 12 units
    - Paddle apparatus at 75 rpm or basket apparatus at 100 rpm
    - Use of surfactants strongly discouraged
Dissolution Definitions

- ‘Very rapidly’ dissolving products
  - Not less than 85% of the labeled amount is released within 15 minutes or less from the test and comparator product
  - In this case, profile comparison is not needed

- ‘Rapidly’ dissolving products
  - Not less than 85% of the labeled amount is released within 30 minutes or less from the test and comparator product
  - Profile comparison (e.g., f2 testing) required
Class III Drug Substances

- Drug substances are highly soluble but limitations to absorption due to various reasons

- Comparison of products (test vs. comparator)
  - Qualitatively the same excipients
  - Quantitatively very similar (as per Level 1 change according to SUPAC)

- Comparative *in vitro* dissolution
  - Not less than 85% dissolved within 15 minutes for both products
Considerations

- Rifampicin containing products are not eligible for a BCS-based biowaiver

- Identification of drug substance eligibility based on solubility, permeability, safety and related properties
  - This does not imply that the comparator product(s) will be very rapidly or rapidly dissolving
  - Very rapidly or rapidly dissolving properties are not required to make an \textit{in vivo} bioequivalence comparison

- BCS-based biowaivers for some FDCs difficult
  - FDC comparator not available
Considerations

- Comparative *in vitro* data surrogate for *in vivo* data
  - Fully developed protocol and operating procedures
  - Complete documentation
  - Biowaiver Application Form: Biopharmaceutics Classification System
  - Monitoring, auditing, inspection