WHO Prequalification Programme

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Prequalification Programme: Priority Essential Medicines
WHO Prequalification Programme

Assessment of bioequivalence studies: Experience from WHO Prequalification Programme
Overview

- Short introduction into the Prequalification Programme
- Bioequivalence
- Biowaivers
- Conclusion
http://apps.who.int/prequal/
UN Prequalification Programme for Priority Essential Medicines

- Action plan of UN from 2001 for expanding access of priority medicines to patients with
  - HIV/AIDS
  - Malaria
  - Tuberculosis
  - Reproductive health
  - Influenza
  - Acute diarrhoea
  - Potentially other categories of products, if there is the need
Elements of Prequalification Programme

Objective:

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

One of the components:

- Evaluation of Quality, Safety and Efficacy of prioritised Essential medicines, inspections of manufacturers and monitoring of the products after their prequalification.
Steps in prequalification

Expression of Interest

Product dossier SMF

Prequalification

Additional information and data

Assessment

Inspections

Corrective actions

Compliance

Maintenance and monitoring

Steps in prequalification

Expression of Interest

Product dossier SMF

Prequalification

Additional information and data

Assessment

Inspections

Corrective actions

Compliance

Maintenance and monitoring
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, The Netherlands .......
Bioequivalence

Multi-source (generic) drug products must satisfy the same standards as those applicable to the originator’s product. In addition, reasonable assurance must be provided that they are, as intended, clinically interchangeable with nominally equivalent market products.
Bioequivalence

Concept: Exposure to the active substance of generic and specialité (innovator) in plasma/blood similar.

Use of pharmacokinetic data to proof therapeutic equivalence.

Therapeutic equivalence of a generic can be assured when the generic is both pharmaceutically equivalent/alternative and bioequivalent.

Concept of interchangeability includes the equivalence of the dosage form as well as for the indications and instructions for use.
Bioequivalence

Different approach for establishing equivalence

PD studies
clinical studies
in vitro methods

ONLY IN EXCEPTIONAL CASE !!
Bioequivalence

- Pharmaceutical equivalence
- Method: in principle comparative pharmacokinetics (AUC, C_{max})
- Acceptance criteria: comparative rate and extent of absorption

90% CI 80 - 125%
Experience

Start difficult for manufacturers and assessors:
- manufacturers: what kind of dossier to be submitted.
- assessors: which criteria to be applied.

Learning process, in which more stringent criteria have been applied during the process.

Better communication, advice and explanation, support by guidance documents (BTIF)
Deficiencies

Overall:

- GLP/GCP
- no bio-study submitted
- insufficient clinical data
- Test and Reference product
- outside the 90% confidence intervals
- Inadequate validation method of the bioanalysis
- no submission of dissolution test
- study design
- outliers
Deficiencies

- GLP/GCP
  - criteria local market ≠ world market
  - GLP
  - fraud
Deficiencies

- insufficient clinical data
  - submission of a clinical study
  - no bioequivalence study submitted
  - dissolution data

learning curve and applying more stringent criteria
Deficiencies

Test and Reference product

EOI:

Invitations for Expressions of Interest (EOIs)

To quality control laboratories

- Quality Control Laboratories - 3rd Invitation for EOI [pdf]

To manufacturers of medicinal products

- HIV/AIDS - 9th Invitation for EOI [pdf]
- Malaria - 8th Invitation for EOI [pdf]
- Tuberculosis - 9th Invitation for EOI [pdf]
- Reproductive Health - 5th Invitation for EOI [pdf]
- Influenza - 2nd Invitation for EOI [pdf]
- Zinc - 1st Invitation for EOI [pdf]

The World Health Organization operates the WHO Prequalification Programme on behalf of the United Nations.

The vision of the WHO Prequalification Programme is of a world in which good-quality medicines are available to all those who need them. The Programme facilitates access to good-quality medicines through assessment of products and inspection of manufacturing facilities. Products that meet assessment criteria are added to the WHO List of Prequalified Medicinal Products. UN agencies and others use the List to guide them in their procurement decisions. Manufacturers of prequalified products may therefore be invited by WHO Member States or UN agencies, or nongovernmental organizations, to submit tenders for supply of their prequalified product (preferably at a preferential price if supply will be to a developing country).

The first step in the prequalification process consists in the joint issuing, by the WHO Prequalification Programme, other UN agencies (UNAIDS and UNICEF) and UNITAID, of an Invitation for Expression of Interest (EOI). EOIs focus on products that have been identified by the respective WHO disease departments as vital to effective treatment and to expanding treatment programmes. Currently, this means products for treating HIV/AIDS, TB and malaria, and for reproductive health. Every product contained in an EOI is already included on the WHO Model List of Essential Medicines and/or in WHO treatment guidelines.

Each EOI invitation may be accompanied by a request for production of the product(s) in a specified quantity and within a specified timeframe.
Deficiencies

Test and Reference product

LIST OF ACCEPTABLE REFERENCE PRODUCTS FOR THE PREQUALIFICATION PROJECT FOR HIV/AIDS MEDICATION

LIST OF ACCEPTABLE REFERENCE PRODUCTS FOR THE PREQUALIFICATION PROJECT FOR ANTIMALARIAL AND ANTITUBERCULOSIS MEDICINES

List of acceptable reference products for the prequalification project for reproductive health

List of acceptable reference products for the prequalification project for Influenza-specific antiviral medicines

Comparator products: Comparator products should be obtained from a well regulated market with stringent regulatory authority i.e., ICH
Deficiencies

outside the 90% confidence intervals

- use of pharmacokinetic data to proof therapeutical equivalence

- pharmaceutical equivalence: quality principle

- applying stringent criteria

90% CI 80 - 125%
## Deficiencies

### Test and Reference product

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>AUC 90% CI Criteria</th>
<th>Cmax 90% CI Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada (most drugs)</td>
<td>80 – 125%</td>
<td>point estimate only</td>
</tr>
<tr>
<td>Europe/FDA (most drugs)</td>
<td>80 – 125%</td>
<td>80 – 125%</td>
</tr>
<tr>
<td>South Africa (most drugs)</td>
<td>80 – 125%</td>
<td>75 – 133% (or broader if justified)</td>
</tr>
<tr>
<td>Japan</td>
<td>80 – 125%</td>
<td>Some drugs wider than 80 – 125%</td>
</tr>
<tr>
<td>Worldwide (WHO)</td>
<td>80 – 125%</td>
<td>80 – 125%</td>
</tr>
</tbody>
</table>
Deficiencies

- inadequate analytical method
  - validation insufficient
  - acceptance criteria analytical run
  - GLP
Deficiencies

- study design
- blood sampling scheme
- parent/metabolite
- power
Prequalified priority essential medicines

Countries where prequalified medicines are manufactured

- India
- France
- South Africa
- UK
- Germany
- Switzerland
- USA
- Canada
- Spain
- Netherlands
- China
- Australia
- Morocco
Biowaivers

Different approach for establishing equivalence

- Standard: in vivo BE studies
- PD studies
- Clinical studies
- In vitro methods
Biowaivers

- Rapid (and similar) Dissolution
- High Solubility
- High Permeability
- Therapeutic Window

Candidates for Biowaivers
Based upon information of the Prequalification Programme experience and applied biowaivers by other NRAs, decision made to select drug substances.

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

- **Medicines for HIV/AIDS and related diseases**
  - Lamivudine (Class I)
  - Stavudine (Class I)
  - Zidovudine (Class I)

- **Anti-tuberculosis medicines**
  - Ethambutol (Class III/I)
  - Isoniazid (Class III/I)
  - Levofloxacin (Class I)
  - Ofloxacin (Class I)
  - Pyrazinamide (Class III/I)
Biowaivers

Guidance:

- Biowaiver application form, identifying clearly what should be submitted.

- Detailed information on Test product (generic)

- Detailed Information on comparator/reference product (identification).

- Comparability between Test and comparator

- In vitro dissolution data

- Quality assurance
Biowaivers

Deficiencies

- Wrong comparator
- Failing comparability regarding excipients
- Failing excluding/including critical excipients
- Failing dissolution tests
Successful BCS-based biowaiver applications have been submitted for HIV/AIDS and anti-tuberculosis products.

Successful BCS-based biowaiver applications for FDCs have been submitted.

BCS-based biowaiver approach for certain drug substances introduced in 2009 - Approaches employed by regulatory authorities considered carefully.

Drug substances on Expressions of Interest being reviewed - Potential additions to list of eligible drug substances.
Conclusions

- Learning process has been fruitful
- Quality of dossiers improved
- Guidance was and is still needed.
- Biowaivers concept applied and biowaivers have been accepted.
Thank you for your attention