HIKMA PHARMACEUTICALS PLC

Regulatory Concepts of Bioequivalence studies and international guidelines

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Regulatory Concepts of Bioequivalence studies and international guidelines

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Outline

■ Rational of conducting BE for marketing authorization of generics.
■ Regulatory requirements
■ Therapeutic equivalents and pharmaceutical equivalent
■ Is there any international Harmonized guidelines
■ Side by side comparison between the four major international guidelines.
■ GCC guidelines
■ Jordan guidelines
■ Morocco guidelines
■ Egyptian guidelines
■ Conclusion
Health care costs continue to increase, and one important component that can be reduced substantially is drug cost.

For this purpose, substitution of the expensive originator drugs with cheaper generic copies is required.

Generic drugs are less expensive than brands as generic manufacturers do not have to conduct costly clinical trials to test the safety and effectiveness.

But ... Generic Copies ...., should be therapeutically equivalent to the brand innovator products
Regulatory Requirements

- All pharmaceutical products, including multisource products, can't be used and freely marketed in a country unless the regulatory authority approves and grants a marketing authorization (registration).

- All required documents should be submitted to prove:
  - Quality
  - Safety
  - And efficacy

- Multisource product must be interchangeable to the originator and **therapeutically equivalent**.
First Product to Market, Reference product

- Innovator’s Product
- Quality
  - Extensive studies to optimize the formulation
- Safety and efficacy
  - Based on extensive clinical trials
  - Expensive
  - Time consuming
Pharmaceutical Equivalents

Possible Differences

- Drug particle size
- Excipients
- Manufacturing Equipment or Process
- Site of manufacture

Could lead to differences in product performance \textit{in vivo}
A “generic product” is a multisource pharmaceutical product which is intended to be interchangeable with the comparator product.

It is usually manufactured without a license from the innovator company and marketed after the expiry of patent or other exclusivity rights.

Bioequivalent drug products are those that show no significant difference in the rate and extent of absorption of the therapeutic ingredient.
Interchangeability

A clinical comparative study which shows therapeutic and side effects should be ideal to show therapeutic equivalence.

- Very large sample size is needed
- Lack of clearly defined and measurable endpoints
- High variability of the measured endpoint

Clinical trials are not the optimum choice for comparisons of formulations with small differences
An alternative method should be developed, which is the **pharmacokinetic approach**.

The advantage of this approach is that
- Clear and Defined endpoint, i.e. the plasma concentration of the drug,
- Lower variability,
- The studies are smaller and more powerful.

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**Therapeutic equivalent (TE) can be reached when the generic copy is bioequivalent (BE) to the brand innovator product**

- *FDA has confirmed on several occasions that bioequivalence requirements for generics and brands are rigorous and ensure that approved generics are therapeutically equivalent to their brand counterparts.*
Pharmaceutical Equivalent and alternative

■ Products are pharmaceutical equivalents:

- If they contain the same molar amount of the same active pharmaceutical ingredient(s) in **the same dosage form** that meet the same or comparable standards and are intended to be administered by the same route.

■ Products are pharmaceutical alternative(s):

- If they contain the same molar amount of the same active pharmaceutical moiety(s) but **differ in dosage form** (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters).
Bioavailability and Bioequivalence

**Bioavailability**:
- The rate and extent to which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

  Reference: Intravenous administration = 100% bioavailability

**Bioequivalence**:
- Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy

  - **Bioequivalence studies are generally recommended**
    - Pharmacokinetic endpoint
    - Pharmacodynamic endpoint
    - Clinical endpoint
    - In vitro endpoint
BE studies are carried out in the following cases:

- **bridging studies**: scale-up from clinical batch to full production scale batch,
- **post-approval changes** in composition or manufacturing process,
- **generic medicine development**.
Is there any international Harmonized guidelines

- **No** there is no International harmonization of regulatory requirements for bioequivalence.
- Bioequivalence range and statistical analysis are to some extent harmonized
- No consensus in
  - Selection of subjects,
  - Food effect,
  - Application of multiple dose study,
  - In vitro dissolution study,
  - Reference product or market leader
  - Two stages or add on studies
FDA guidance

- **Guidance for Industry** /Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revised) (I) 3/19/2003
- **Guidance for Industry** /Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action DRAFT GUIDANCE /FDA April 2003
- **Guidance for Industry** /Food-Effect Bioavailability and Fed Bioequivalence Studies /Dec 2002
- **Guidance for Industry**/Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (I) 8/31/2000
- **Guidance for Industry**/Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action
Bioequivalence Recommendations for Specific Products

- Bioequivalence Recommendations for Specific Products (PDF - 81KB) (Issued June 2010)
- Dissolutions Methods Database

"Please submit comments for any of the guidances posted in the Bioequivalence Recommendations for Specific Products website to the Division of Dockets Management (DDM) under Docket FDA-2007-D-0369-0015. For electronic comments refer to the website http://www.regulations.gov OR you can mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Please contact the Regulations.gov HelpDesk at 1-877-378-5457 (toll free) for assistance regarding submissions."

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 1026]

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Newly Added Recommendations - September 2012 (44 News, 10 Revision) updated 11/5/2013
EMA guidelines

- GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

- GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) London, 22 January 2009
  Doc. Ref. CPMP/EWP/4151/00 Rev. 1

- GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE
  Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1 REV. 1 DATE FOR COMING INTO EFFECT 1 August 2010

- This guideline will replace the “Note for guidance on the investigation of bioavailability and bioequivalence” CPMP/QWP/EWP/1401/98 and the related questions in the Q&A document (CHMP/EWP/40326/06).
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

WHO requirements

  Multisource (generic) pharmaceutical products:
  guidelines on registration requirements to establish
  Interchangeability

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

  Additional guidance for organizations performing
  in vivo bioequivalence studies

  Guidelines for registration of fixed-dose combination medicinal products

GUIDANCE DOCUMENT
Conduct and Analysis of Comparative Bioavailability Studies


LIGNE DIRECTRICE
Conduite et analyse des études de biodisponibilité comparatives

Canadian Guidelines

- Notice to Industry: Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005).

- **All these guidelines are superseded by two guidance issued 2012 and implemented July 2012**
Objectives of Guidance

<table>
<thead>
<tr>
<th>Country</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>BE studies are undertaken in support of ANDA submissions with respect to 21 CFR part 320. FDA</td>
</tr>
<tr>
<td>EMA</td>
<td>To support the marketing Authorization Applications for human medicinal products submitted in accordance with the Directive 2001/83/EC as amended, under Art. 10 (1) (generic applications) to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product</td>
</tr>
<tr>
<td>Canada</td>
<td>To submit new generic drug which complies with Sections C.08.002(2)(h), C.08.002.1(2)(c)(i) and C.08.003(3) of the Food and Drug Regulations (Regulations) with respect to comparative bioavailability studies used in support of the safety and efficacy of a drug, issued July 2012</td>
</tr>
<tr>
<td>WHO</td>
<td>These guidelines are intended to provide recommendations to sponsors on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. WHO Technical Report Series, No. 937, 2006, Annex 7.</td>
</tr>
</tbody>
</table>
## Scope of the guidance

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>Product-specific BE recommendations depending upon the novelty and complexity of the scientific considerations</td>
</tr>
<tr>
<td>EMA</td>
<td>Recommendations for bioequivalence studies for immediate release formulations with systemic action</td>
</tr>
<tr>
<td>Canada</td>
<td>Guidance is oriented toward solid oral dosage formulations, both immediate, modified-release, and any dosage forms that are intended to deliver medication to the systemic circulation.</td>
</tr>
<tr>
<td>WHO</td>
<td>Applicable to orally administered multisource products, non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products)</td>
</tr>
</tbody>
</table>
## Legal enforcement

<table>
<thead>
<tr>
<th>Country</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>Non binding recommendation, do not establish legally enforceable responsibilities</td>
</tr>
<tr>
<td>EMA</td>
<td>Provide recommendations for BE studies of immediate release dosage forms with systemic action, the design, conduct, evaluation and bio-waivering</td>
</tr>
<tr>
<td>Canada</td>
<td>Guidance is provide assistance to industry and health care professionals, its administrative not having force of law and allow flexibility in approach.</td>
</tr>
<tr>
<td>WHO</td>
<td>No enforcement of the guidelines</td>
</tr>
</tbody>
</table>
Clinical ethical principles

**FDA**
(CRO) sites are most often subject to GCP inspections with reference to 21 CFR Parts 11/50/54/56//58/312 and 314 for the FDA.

**EMA**
The reference GCP standard for the inspections will be ICH Topic E6: Guideline for Good Clinical Practice, the Clinical Trial Directive 2001/20/EC for the EMEAEMEA (GCPs, GLPs, new draft guidance on BE, http://www.emea.europa.eu/pdfs/human/gvp/140198enrev1.pdf

**Canada**
Same as EMA, ICH Topic E6: Guideline for Good Clinical Practice.

**WHO**
WHO guidelines for good clinical practice GCP
# Reference product

| **FDA** | A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA |
| **EMA** | Reference medicinal product marketed in the EU. Bioequivalence studies comparing the product applied for with non-EU reference products should not be submitted. |
| **Canada** | Drug in respect of which a notice of compliance is issued and which is marketed in Canada by the innovator of the drug; or a drug, which is acceptable to the Minister, that can be used for this purpose |
| **WHO** | The selection of the comparator product is usually made at the national level by the drug regulatory authority. |
Test product and biobatch

**FDA**
- Pilot batch 1/10 of production, prepared at the same manufacturing site to be marketed later or equivalent site

**EMA**
- Pilot Batch, 1/10 of commercial, and if less full production batch to be used
- Assay difference between test and reference not more than 5%
- Follow GMP

**Canada**
- Pilot batches, minimum of 10% of the commercial batch size or 100,000 units unless otherwise justified
- The lots should be produced using the same type of equipment and procedures, and for modified-release formulations, the same site, as proposed for market production
- Follow GMP requirements

**WHO**
- Assay difference between test and reference not more than 5%
- Pilot or small-scale production batches may be used, 1/10 of commercial, and if less full production batch to be used, using same type of equipment
- Follow GMP
Subjects

FDA
Minimum of 12 subjects

EMA
Number of subjects to be included in the study should be based on an appropriate sample size calculation. The number of evaluable subjects in a bioequivalence study should not be less than 12. Two-stage studies are permitted calculating the 94.12% confidence interval instead of 90%

Canada
Minimum of 12 is accepted, but larger number is required add on studies are permitted.

WHO
The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design. Large numbers in studies of highly variable drugs to achieve adequate statistical power.
<table>
<thead>
<tr>
<th>Country</th>
<th>Bioequivalence Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA</td>
<td>AUC, Cmax 80-125% for all, truncated is possible for API with long half life. Narrow therapeutic product 90-111%. Highly variable CV% more than 30%, wider Cmax permitted with different statistical approach.</td>
</tr>
<tr>
<td>EMA</td>
<td>(AUC0-t), the area under the plasma, concentration-time curve from 0 to infinity, AUC0-∞, the residual area (AUCt-∞), the maximum plasma concentration (Cmax) and the time at which Cmax was observed (Tmax). 80-125%, truncated is possible for long half life. For highly variable wider limits are permitted, for CV values of 50% or higher, the 90% BE acceptance limits are capped at 69.84 – 143.19%. No consensus between EU countries.</td>
</tr>
<tr>
<td>Canada</td>
<td>AUC, Cmax 80-125% for all Narrow therapeutic product and critical dose drugs 90-112%. Truncated 72 hrs accepted. Highly variable CV% more than 30%, wider Cmax permitted with different statistical approach, two stages studies are permitted for once.</td>
</tr>
<tr>
<td>WHO</td>
<td>AUC and Cmax 80-125%, Truncated AUC 0-72 is accepted for long half life products. NTI, API 90-111% is the 90% confidence limit. Wider Cmax limits is accepted for highly variable drug products.</td>
</tr>
<tr>
<td>Agency</td>
<td>Requirement</td>
</tr>
<tr>
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<td>--------------------------------------------------</td>
</tr>
<tr>
<td>FDA</td>
<td>Fed and Fast for all, with some addition steady state studies</td>
</tr>
<tr>
<td>EMA</td>
<td>Fast studies in general except for modified release and those should be taken with food as per the SmPC of originator</td>
</tr>
<tr>
<td>Canada</td>
<td>Fast studies for immediate, and both fed and fast for modified</td>
</tr>
<tr>
<td>WHO</td>
<td>As per EMA guidelines</td>
</tr>
</tbody>
</table>
Bio-waivers

- All guidelines agreed that the following can be bio-waived from submission bioequivalence studies:
  - Parenteral aqueous solutions
  - Locally acting locally applied products (after oral, nasal, pulmonary, ocular, dermal, rectal, vaginal etc. administration)
  - Gases
  - BCS-based Biowaiver, class 1
  - Lower strengths if linear kinetic and proportionality in composition

- While Class III biowaived by EMA guidance and WHO guidance
With regard to regulations covering BE studies in some Arab countries has published their own guidelines like:

- GCC
- Jordan
- Egypt
- Morocco

Others follow EMA or FDA guidelines as internal policy in the authority.
GCC requirements

- The GCC Guidelines for Bioequivalence/Version 2/ Date of implementation 3/05/2011
- This guideline is adapted from the EMEA guideline on the investigation of bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/
- Guidelines for Biowaiver /Draft /Based on Biopharmaceutics Classification System (BCS) For Immediate-Release (IR) Solid Oral Dosage Forms /date of implementation 12/2012
- Objectives: to specify the requirements for the design, conduct, and evaluation of bioequivalence studies, and the possibility of using in vitro instead of in vivo studies.
- Scope: focuses on recommendations for bioequivalence studies for immediate release formulations with systemic action and biowaivers.
- Outsourced bioequivalence studies are not accepted unless fully imported product.
GCC continued

- **Reference product**: The selected reference drug would normally be the original brand-name registered in the GCC. When the original brand-name is not registered in the GCC, the original brand-name registered in USA or Europe may be used as a reference product, or the available market leader.

- **Test product**: pilot batches 1/10 of production batch, if less full scale production batch.

- **Subjects**: A number of subjects of less than 24 may be accepted (with a minimum of 18 subjects) when statistically justifiable.

- **Parameters**:
  - 80-125% for AUC and Cmax
  - 90-111.11% for narrow therapeutic index
  - 75-133% for highly variable products for Cmax

- **Biowaivering**: matches with EU guidance except for Class III as it's not a biowaiver.
Jordan BE requirements

- Jordan Guidelines and criteria of evaluation of Bioequivalence studies / Date of implementation 30/8/2010

- **Objectives**: to specify the requirements for the design, conduct, and evaluation of bioequivalence studies, and the possibility of using *in vitro* instead of *in vivo* studies.

- **Scope**: focuses on recommendations for bioequivalence studies for all formulations with systemic action unless biowaived according to the guidelines.

- The guidelines specify the content and format of the BE study as check list

- **Outsourced Bioequivalence** studies are accepted as technology transfer with extra comparative dissolution studies

- **The guidelines did not interfere with any technical requirements of the study**, as the design, study conduct, statistical analysis, parent or metabolites, but the study should be refer to a recognized reference guidelines and scientifically justified
Jordan guidelines

- **Reference product**: The selected reference drug would normally be the original brand-name known worldwide or the market leader

- **Test product**: pilot batches 1/10 of production batch, if less full scale production batch

- **Subjects**: A number of subjects of less than 24 may be accepted (with a minimum of 18 subjects) when statistically justifiable

- **Parameters**:
  - 80-125% for AUC and Cmax
  - 90-111.11% for narrow therapeutic index
  - Highly variable as per EMA guidelines

- **Biowaivering**: Class I and Class III

- **Dissolution requirements**: well defined in the guidelines
Morocco requirements

- New requirements issued in 12 June 2012
- Will be implemented in 12 Dec 2012
- The guidance does not fully follow international reference guidance as EMA 2010 guidance
- Scope: covers all generic products IR or MR, locally manufactured or imported
Morocco ...., BE needed for

- Oral immediate release forms with systemic actions
- Products with potent API
- Products contain Narrow therapeutic index API
- Well known problematic products.
- Has complicated physiochemical properties
- Topical products that shouldn’t be absorbed
- Modified release products
- Combination products, where any of the APIs needs BE
- Non oral, nor injectable Products with systemic action
Morocco .....Biowaivers

- All aqueous pharmaceutical presentations.
- Class 1 products
- Proportional lower concentrations of IR products
- Gases
- Similar products to already approved marketed products by MOH where they have same API source as reference product.
Morocco …..Major issues

■ Reference product:
  – The reference marketed in Morocco
  – If not marketed originator reference product can be used
  – First product approved through submission clinical studies and marketed in Morocco.

■ Bio batch size
  – Local products: Should be done on the first industrial batch which fully complies with the specification approved by MMOH
  – Imported products: Industrial or commercial batch size

■ According to the guidance (article 8) sponsor of the BE study should be Moroccan company.
EGYPT Requirements

- Issued 2008 with reference to WHO guidelines
- **Subjects**: not less than 24, larger for highly variable
- **Limits accepted**: For $\text{AUC}_{0\rightarrow t}$ and $\text{AUC}_{0\rightarrow \infty}$ confidence interval should be between 80% and 125%. For $\text{C}_{\text{max}}$ the confidence intervals should be between 70% and 143% for highly variable products.
- List of approved CROs (Egyptian) are published
- **Reference**: the reference product registered in Egypt
- **Test product**: should be manufactured at the Egyptian facility
Conclusions

- No harmonized bioequivalence guidelines either internationally, nor in Arab countries.
- Cost of the product will increase as sometimes more than one bioequivalence study is conducted to match the regulation.
- EU and US FDA are working together toward harmonization of the ethical requirements, and to share information on inspections and GCP-related documents of common interest and to conduct collaborative inspections/paper concept July 2011.
- More work from regulatory bodies is needed toward mutual recognition of CROs, to develop more harmonized regulations.
Thank you