HIKMA PHARMACEUTICALS PLC

Regulatory Concepts of Bioequivalence studies and international guidelines

6th Dec 2012

Regulatory Concepts of Bioequivalence studies and international guidelines

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6th Dec 2012

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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

Rational

- 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

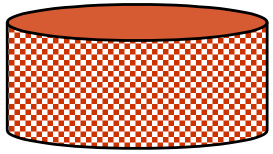
- All pharmaceutical products, including multisource products, can't be used and freely marketed in a country unless the regulatory authority approves and grants a marketing authorization (registration)

- All required documents should be submitted to prove :
  - Quality
  - Safety
  - And efficacy
- Multisource product must be interchangeable to the originator and **therapeutically equivalent**.

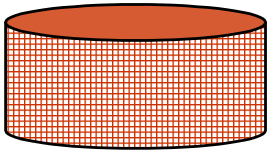
First Product to Market ,Reference product

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

Pharmaceutical Equivalents



Test



Reference

Possible Differences

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

Could lead to differences in product performance *in vivo*

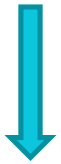
Generic product

- 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

Interchangeability continued

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.

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

Why Bioequivalence studies are conducted ?

- BE studies are carried out in the following cases:

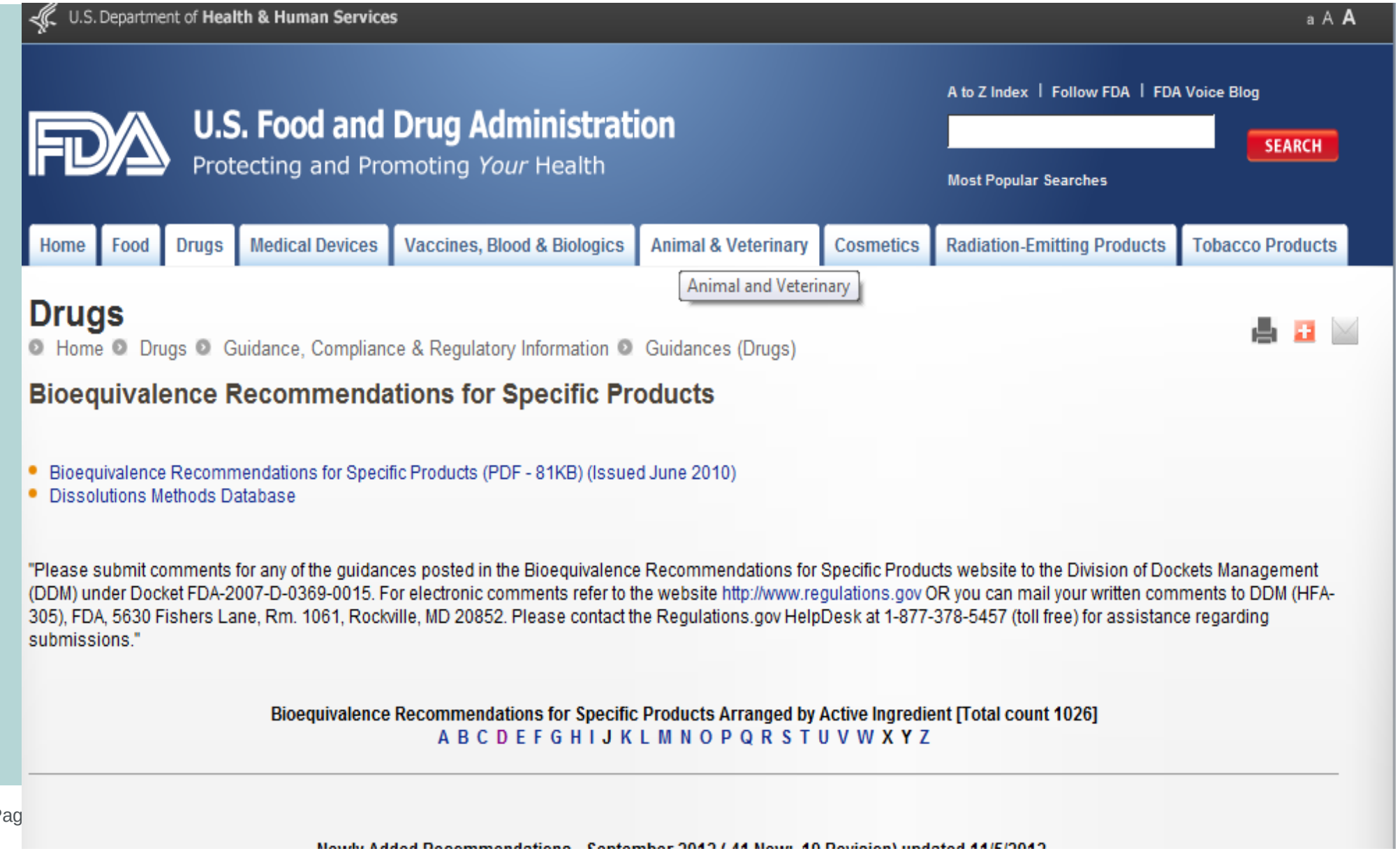
  - ***bridging studies***: scale-up from clinical batch to full production scale batch,
  - ***post-approval changes*** in composition or manufacturing process,
  - ***generic medicine development***.

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
- ***Guidance of Industry/ Individual Product Bioequivalence Recommendations - List of Product Bioequivalence Recommendations (I) 6/11/2010***
- (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm



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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 11/5/2012

EMA guidelines

- **GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE**

  Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1**First guidance issued January 2002**

- G**UIDELINE 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. 1REV. 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*).**

EUROPEAN MEDICINES AGENCY (EMA)

European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

WHO requirements

- World Health Organization /WHO Technical Report Series, No. 937, 2006 /Annex 7
  Multisource (generic) pharmaceutical products:
  guidelines on registration requirements to establish
  Interchangeability
- WHO Technical Report Series, No. 937, 2006 /Annex 8
  Proposal to waive in vivo bioequivalence
  requirements for *WHO Model List of Essential*
  Medicines immediate-release, solid oral dosage forms
- World Health Organization/WHO Technical Report Series, No. 937, 2006 *Annex 9
  Additional guidance for organizations performing
  in vivo bioequivalence studies
- World Health Organization /WHO Technical Report Series, No. 929, 2005/Annex 5
  Guidelines for registration of fixed-dose combination medicinal products
- *http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937_e*

HEALTH CANADA – SANTE CANADA

Health Canada Santé Canada

GUIDANCE DOCUMENT

Conduct and Analysis of Comparative Bioavailability Studies

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.pdf

LIGNE DIRECTRICE

Conduite et analyse des études de biodisponibilité comparatives

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-fra.pdf

Canadian Guidelines

- *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects* (1992).
- Report C (of the Expert Advisory Committee on Bioavailability and Bioequivalence): Report on Bioavailability of Oral Dosage Formulations, Not in Modified Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics (1992).
- *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations* (1996).
- *Draft Policy: Bioequivalence Requirements: Drugs Exhibiting Non-Linear Pharmacokinetics* (2003).
- Notice to industry: Removal of Requirement for 15% Random Replicate Samples (2003).
- *Draft Guidance for Industry: Use of Metabolite Data in Comparative Bioavailability Studies* (2004).
- Notice to industry: Bioequivalence requirements for combination drug products (2004).
- *Guidance for Industry: Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State* (2005).
- 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).
- Notice to Industry: Bioequivalence Requirements for Long Half-life Drugs (2005).
- *Guidance for Industry: Bioequivalence Requirements: Critical Dose Drugs* (2006).
- **All these guidelines are superseded by two guidance issued 2012 and implemented July 2012**

Objectives of Guidance

FDA	BE studies are undertaken in support of ANDA submissions with respect to 21 CFR part 320. FDA
EMA	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
Canada	To submit new generic drug which complys with Sections C.08.002(2)(h), C.08.002.1(2)(c)(ii) 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
WHO	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.*

Scope of the guidance

FDA	Product-specific BE recommendations depending upon the novelty and complexity of the scientific considerations
EMA	Recommendations for bioequivalence studies for immediate release formulations with systemic action
Canada	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.
WHO	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

Legal enforcement

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

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/qwp/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

Bioequivalence parameters

FDA	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
EMA	(AUC0-t), the area under the plasma, concentration-time curve from 0 to infinity ,AUC0-∞), the residual area (AUCt-∞), the maximum plasma concention (Cmax) and the time at which Cmax was observed (T max).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
Canada	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 .
WHO	AUC and C max 80-125% , Truncated AUC 0-72 is accepted for long half life products NTI ,API 90-111% is the 90% confeidence limit Wider Cmax limits is accepted for highly variable drug products

Food effect studies

FDA	Fed and Fast for all ,with some addition steady state studies
EMA	Fast studies in general except for modified release and those should be taken with food as per the SmPC of originator
Canada	Fast studies for immediate ,and both fed and fast for modified
WHO	As per EMA guidelines

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

Arab countries guidelines

- 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 its 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 the be Moroccan company .

EGYPT Requirements

- Issued 2008 with reference to **WHO guidelines**
- **Subjects** : not less than 24 ,larger for highly variables
- Limits **accepted** : For $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$confidence interval should be between 80% and 125%.For C_{max} the confidence intervals should be between 70% and 143% for highly variable products .
- list of **approved CRO** s(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