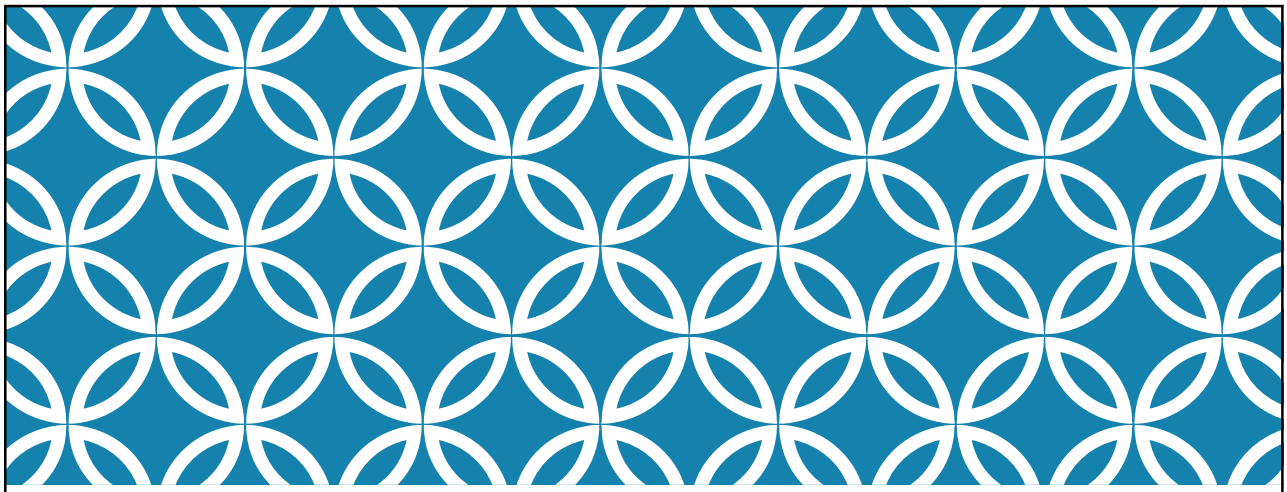
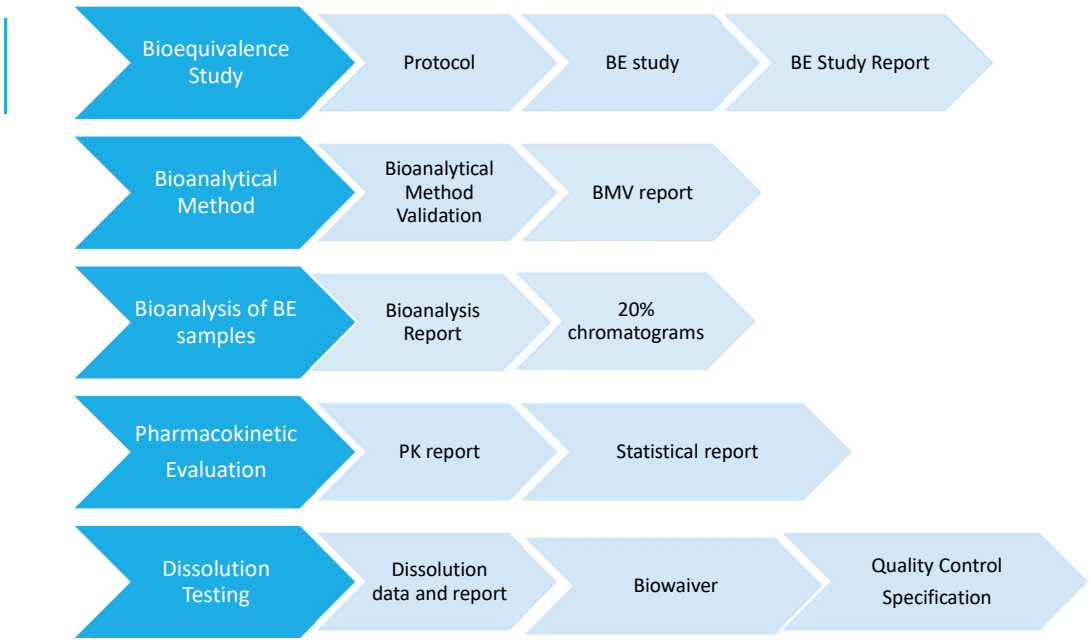


INTRODUCTION TO BIOEQUIVALENCE STUDIES

Loice Kikwai
BE Webinar Training

DISCLAIMER

- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration or the Saudi Food and Drug Authority



OUTLINE

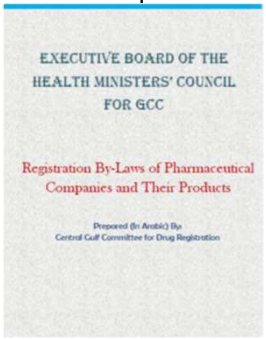
- Regulatory authority on bioequivalence (BE)
- Principles of Bioequivalence
- Definitions of key Bioequivalence terms
- Why BE studies are requested
- Approaches to determine bioequivalence
- Designing a Bioequivalence study

REGULATORY AUTHORITY ON BE

- All agencies of Ministries of Health, have regulatory authority to regulate the drug products that are marketed within its borders
  - FDCA (§505(j)) states that rate and extent of drug absorption must be compared to establish bioequivalence between two products
  - Directive 2001/83/EC as amended, under Art. 10 (1) (generic applications).
    - Marketing Authorisation Applications for human medicinal products submitted under Art. 8(3) (full applications), Art. 10b (fixed combination), Art. 10(3) (hybrid applications) of the same Directive,
    - Commission Regulations (EC) No 1084/2003 and 1085/2003: extension and variation

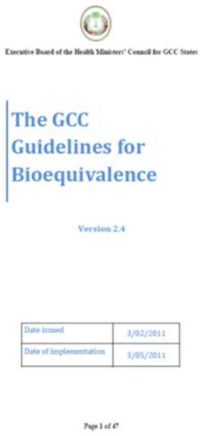
مجلس الصحة
لدول مجلس التعاون
Gulf Health Council

- Guidelines:
  - http://ghc.sa/en-us/Pages/modawanat.aspx
- GCC - Guidelines for Bioequivalence version 2.4


EXECUTIVE BOARD OF THE HEALTH MINISTERS' COUNCIL FOR GCC

Registration By-Laws of Pharmaceutical Companies and Their Products

Prepared (In Arabic) By
Central Gulf Committee for Drug Registration


Executive Board of the Health Ministers' Council for GCC States

The GCC Guidelines for Bioequivalence

Version 2.4

Date issued	3/02/2011
Date of implementation	3/05/2011

Page 1 of 47

DEFINITIONS AND PRINCIPLES

- Good Clinical Practice (GCP): A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting, and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic, or prophylactic) under investigation are properly documented.
- Good Laboratory Practice* (GLP): A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported (OECD/WHO).
  - *as applied to human bioanalysis studies
- Contract Research Organization (CRO): A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

WHY AGENCIES REQUESTS BE STUDIES

- To determine rate/extent of absorption of each therapeutic moiety for
  - Potential generic products for which there is a reference listed drug (RLD) approved for marketing
  - Potential new drug products (new salts, dosage forms) for which adequate clinical studies have already been conducted
  - Reformulated drug products

DEFINITIONS AND PRINCIPLES***

- Bioavailability (BA): The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed in to the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.
- Bioequivalence (BE): The absence of significant differences in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered in the same molar dose under similar conditions in an appropriately designed study.

DEFINITIONS AND PRINCIPLES

- Bioequivalence (BE): Two pharmaceutical products are bioequivalent if they are pharmaceutically **equivalent** or pharmaceutical **alternatives**, and their bioavailabilities, in terms of peak (Cmax and Tmax) and total exposure (area under the curve (AUC)) after administration of the same molar dose under the same conditions, are similar as to such a degree that their effects can be expected to be essentially the same.
  - http://apps.who.int/medicinedocs/documents/s22406en/s22406en.pdf

DEFINITIONS AND PRINCIPLES

- Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules).

- Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules).

  - https://www.boomer.org/c/p4/c10/c1002.php

DEFINITIONS AND PRINCIPLES

- Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Interchangeable!!!
- (1) Safe and effective
- (2) Pharmaceutical equivalents:
  - (a) identical amounts of the same active drug ingredient in the same dosage form and route of administration,
  - (b) meet compendial or other applicable standards of strength, quality, purity, and identity
- (3) Bioequivalent
  - (a) NO BE problem, should meet an acceptable in vitro standard
  - (b) Potential BE problem, should meet an appropriate bioequivalence standard
- (4) Adequately labeled
- (5) Manufactured in compliance with Current Good Manufacturing Practice

DEFINITIONS AND PRINCIPLES

- Generic product: pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of patent or other exclusivity rights.
- Reference product: pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product would normally be the innovator product for which efficacy, safety and quality have been established.
  - When the innovator product is not available the product which is the word market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

DEFINITIONS AND PRINCIPLES

- Innovator pharmaceutical product: is one, authorized for marketing (normally as a patented drug) on the basis of documentation of efficacy, safety and quality.
- Interchangeable pharmaceutical product: is one, which is therapeutically equivalent to a reference product.
- Multi-source pharmaceutical products: are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multi-source pharmaceutical products that are therapeutically equivalent are interchangeable.

DEFINITION AND PRINCIPLE

- Biowaiver
  - The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing
- Equivalence test
  - A test that determines the equivalence between the multisource product and the comparator product using in vivo and/or in vitro approaches

DEFINITIONS AND PRINCIPLES

- What is Bioequivalence?
  - Comparison of two products with respect to rate and extent of drug availability.
- Why Bioequivalence?
  - For product approval and to establish interchangeability
    - products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- When is Bioequivalence needed?
  - To establish BE between a clinical batch and a to-be-marketed batch
  - To compare BA between the comparator and multisource products

APPROACHES TO DETERMINE BIOEQUIVALENCE

- Listed in descending order of accuracy, sensitivity, reproducibility
  - Pharmacokinetic (PK) study in which drug concentrations are measured in plasma
    - In vitro-in vivo correlation (IVIVC)
  - PK study in which drug concentrations are measured in urine
  - Acute pharmacological effect measured as a function of time - BE study with pharmacodynamic (PD) endpoints
  - Well-controlled clinical trial in humans (BE study with clinical endpoints)
  - Currently available in vitro test, that ensures bioavailability (BA)

WHEN BIOEQUIVALENCE STUDIES ARE NECESSARY

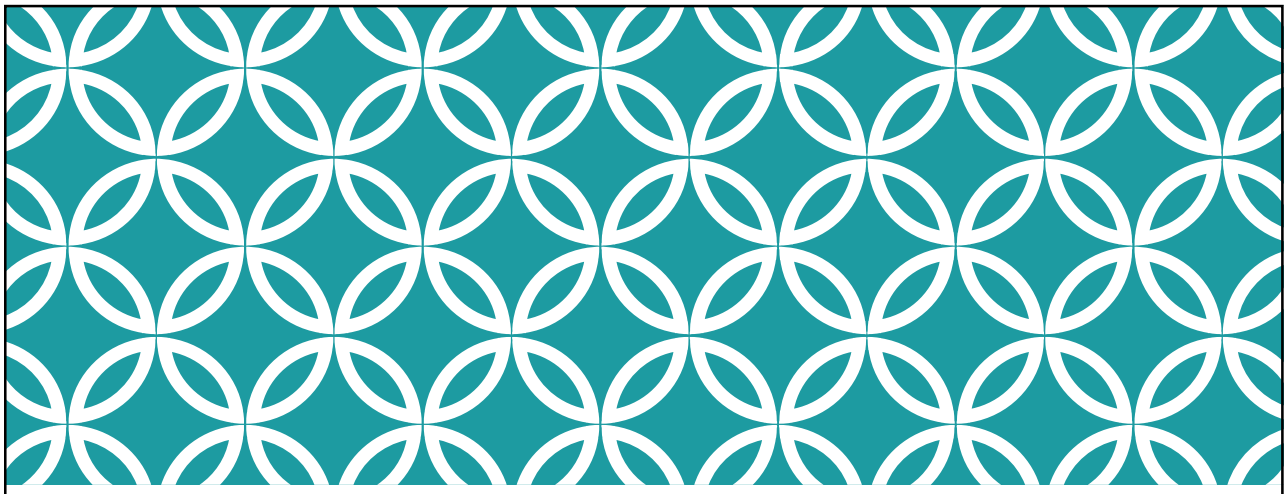
- Oral Immediate Release products
  - Critical use medicines
  - Narrow therapeutic range drug products
  - Documented BA or BE problems related to API
  - Scientific evidence suggesting polymorphs of API, excipients, and/or process affecting BA
- Non-oral, non-parenteral products designed to act systemically
- Oral Modified Release products
- Fixed-combination products with systemic absorption where at least one of the API requires an in vivo study

IN VIVO BE STUDIES

- In vivo documentation of equivalence through either
  - Comparative Pharmacokinetic study
  - Comparative Pharmacodynamic study (more variable than PK)
  - Comparative Clinical trial (Required when PK and PD studies can't be performed. Methodology not yet well established as for PK study)
- In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

WHEN EQUIVALENCE STUDIES ARE NOT NECESSARY

- Bioequivalence studies in general are not necessary for
  - Parenteral preparations – aqueous solutions
  - Solutions for oral use
  - Powders for reconstitution as a solution
  - Gases
  - Otic or ophthalmic products prepared as aqueous solutions
  - Topical products prepared as solutions
  - Aqueous solutions for nebulizer inhalation or nasal sprays



DESIGNING A BE STUDY

ETHICS PRINCIPLES

- All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki.
- It is essential to have a review committee confirm the protocol complies with ethical standards for research on human subjects.
- The voluntary informed written consent of the healthy volunteers to participate in the study must be obtained.
- Information given to each volunteer should include details of the study, risks associated with participation and information regarding the right to withdraw at any time from participation without jeopardy.

ETHICS

- IEC / IRB: ICH Definition
  - An independent body of medical, scientific and non-scientific members
  - Responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial
    - Reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects;
    - Independent "Risk-benefit" evaluation

ETHICS

- Composition requirements ICH GCP
  - At least 5 members
  - At least one member whose primary area of interest is a non-scientific area
  - At least one member who is independent of the trial site
  - Members without conflicting interest
    - Only those members independent of the investigator and the sponsor should review on a trial-related matter
- Required documents
  - Protocol (signed at least by the principal investigator)
  - Patient Information Sheet/Consent Form
  - Investigator´s Brochure
  - Subject recruitement procedures (e. g. advertisements)

ETHICS

- Approval notification to Investigator
- Timely written approval
  - Identification of study (title, protocol number, version, investigator, site)
  - Specify all items reviewed
  - Date & place of review
  - Trial/study related decisions
  - Reasons for modifications & disapprovals
- Minimum information required by ICH-GCP:
  - Date of the meeting
  - Documents reviewed (versions & dates)
  - List of members

THE COMPARATORS OR REFERENCE PRODUCT

- Comparator
  - WHO publishes list of comparators
  - Comparators for second line TB product
  - Comparators should be obtained from the source stated in the list of comparators (well regulated market)
    - Countries in the ICH members (US, EU, Japan), ICH observers and associated members
    - There are instance where the product can be sourced from non-ICH region eg. SA for Terrizidone
  - Traceability (invoice, shipment record, Labelling, CoA, applicant QA authenticity etc)
    - This is when used for the purpose of BE/BW study. For the purpose of pharmaceutical development work CoA of the comparator reported in under formulation development will suffice but wise to get the product from well regulated source to avoid bias.

THE TEST PRODUCT

- The test product used in the BE study = the Bio batch
- The bio batch of the test product could be
  - Proposed production batch size
  - Adequate pilot batch size that can scaled for scale up
    - Bio batch should be >100,000 or NLT 1/10th of production scale
      - But if BE is performed on batch size of 100,000units then production batch size can't be scaled up beyond 1000,000units
    - For injectable product the pilot scale should be less than 10% of production batch size
      - Example, if the proposed batch size is 60,000 vials, then pilot scale (bio-batch) could be ≥6,000vials
        - Difficulty in setting one fixed proposed batch size for injectable preparation due to complexity of manufacturing process
        - The purpose of the pilot scale in aqueous injection is mainly for development works (validation, stability, formulation, etc)

PHARMACOKINETIC…

- The lot number of reference and test product should be stated, both should have the same age, not more than 5% difference in assay value
- Prior to and during each study phase
  - Water is allowed as desired (except 1hr before and after drug administration)
  - Standard meal no less than 2hr after administration of drug
  - Abstain from alcohol for 24hr prior to each period and until after the last sample from each period is collected

PHARMACOKINETIC BIOEQUIVALENCE STUDY

Type of Study

- Fasting
- Fed
  - Labeling
  - Steady State Safety consideration: chemotherapy agents, antipsychotics, etc.
  - Patients who are already receiving the medication
- Sprinkle
  - Capsules

Study Design

- Standard design: randomized, two-period, two-sequence, single dose cross over design
  - Adequate washout period: more than five T1/2
- Alternative design:
  - Parallel: drug products with very long half-life
  - Replicate: highly variable drug products

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STUDY DESIGN

❑A two-period, two sequence, single dose, cross-over, randomized design in healthy volunteers (2X2)

	Period 1	Washout (passive)	Period 2
Sequence 1 (AB) (n subjects)	Comparator product	>5 half-lives	Multisource product
Sequence 2 (BA) (n subjects)	Multisource product		Comparator product

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STUDY DESIGN

Other design when justified

- Multiple dose instead of single dose
  - for less sensitive method
- In patients instead of healthy subjects
  - if single dose in healthy subject is not tolerable
- Fasting state vs fed state condition
  - When the product is to be administered with a special meal or fast state (refer to innovator SmPC)
- Parallel design instead of randomized crossover
  - For larger half lives (>4weeks)
  - High variability
- Replicate design vs 2X2
  - For highly variable drugs (CV >30%)

STUDY DESIGN

- ❑Sufficient washout between period to avoid carry over
- ❑Blood samples are collected and assayed
  - Before and several times after drug administration up to 72hr
- ❑Prior to the next dose (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)
- ❑Fasted study is the norm (SmPC of innovator is the guide)

PHARMACOKINETIC BIOEQUIVALENCE STUDY

Bio-strength

- Typically highest strength
- Sometimes lower strength due to safety concern
  - e.g.: Aripriprazole Orally Disintegrating Tablets:
    - fasting and fed studies on 10 mg; waiver on 15, 20 and 30 mg
    - 15 mg and 30 mg strengths: poorly tolerated by healthy voluneers; life-threatening acute laryngeal dystonia on a single dose of 30 mg
- Sometimes can be more than one strengths
  - e.g.: Nisoldipine ER Tablets: fasting and fed studies on 40 mg; a fasting study on 30 mg; waiver on 20 mg

Subjects:

- Normal healthy adults, male and/or female
- Patients

Analyte to measure

- Parent drug and /or active metabolite
- Basis of the bioequivalence (90% CI)

STUDY STANDARDIZATION

- Standardization of study conditions is important to minimize the magnitude of variability other than in the pharmaceutical products
- Standardization should cover:
  - Exercise
  - Diet
  - fluid intake
  - Posture
  - Restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified time period before and during the study
- Volunteers should not take any other medicine, alcoholic beverages or over the-counter (OTC) medicines and supplements for an appropriate interval either before or during the study

STUDY STANDARDIZATION

- In the event of emergency, the use of any non-study medicine must be reported (dose and time of administration).
- Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility
- The same pattern of posture and activity should be maintained for each day of the study
- The time of day at which the study drug is to be administered should be specified
- All meals should be standardized and the composition stated in the study protocol and report.

PHARMACOKINETIC…

- Single dose study is considered more sensitive in assessing release of the drug substance from the drug product into circulation for both IR and MR product
  - A multiple-dose study for MR dosage form may be requested if single dose study is not satisfactory
- Study Requirements:
  - A single dose fasting study comparing highest strength of multisource and comparator (T and R) products
  - A single dose food-effect study comparing highest strength of multisource and comparator (T and R) products when there is known Food-Drug interaction

FASTING AND FED CONDITIONS

- Fasting state studies are generally preferred
  - Labeling only on an empty stomach, or
  - Labeling irrespective of food intake
- Fed state:
  - When the product is known to cause gastrointestinal disturbances in the fasted state, or
  - If labeling restricts administration in the fed state
- Composition of meal may depend on local diet and customs

FASTING CONDITION

- Most sensitive and discriminating form of BE study design
- Single-dose fasting BE study for all systemically available/active drugs
- Unless precluded for safety reasons
- Overnight fast of at least 10 hours
- Participants are allowed free access to water
- No water is allowed during the hour prior to drug admin.
- The dose should be taken with a standard volume of water
  - Usually 150–250 ml.
- 2 hrs after drug administration water is permitted
- A standard meal is usually provided 4 hrs after drug administration

FED STUDY

- BE study should be conducted for all orally administered immediate release (IR) drug products with the exceptions:
  - When the RLD label clearly indicates that the drug should be taken on empty stomach; or
  - A study population of cancer patients has difficulty in successfully ingesting a high fat meal; or
  - A fed study would cause safety or efficacy concerns.
- For most solid oral dosage forms, sponsor should conduct both fasting & fed BE studies
- Drug is given within 30 minutes of consuming a high-fat meal
- Meal should provide 800-1000 Kcal in total and at least 50% of the total Kcal from fat
- Standardized meal description
  - Non-standardized meal is acceptable if meets total Kcal and fat Kcal criteria

SAMPLE FLUIDS AND THEIR COLLECTION

- Usually blood should be the biological fluid sampled
- In most cases the analyte is measured in serum or plasma
- Urine only if the analyte cannot be measured in plasma, etc.
  - The volume of each sample must be measured at the study centre, where possible immediately after collection, and included in the report
  - In most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the tmax and Cmax
- Samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes
- The sample collection methodology must be specified in the study protocol.

SAMPLING

- Blood samples with frequency sufficient for assessing Cmax, AUC and other parameters

- Sampling points should include:
  - a pre-dose sample,
  - at least 1–2 points before Cmax,
  - 2 points around Cmax and
  - 3–4 points during the elimination phase.
  - Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters

BIOEQUIVALENCE STUDY

- How long should you collect blood samples in BE study?
  - In general for 3 or more terminal half lives
  - For long half life drugs for 72 hours
- What should be measured in BE studies - Parent drug and/or metabolites?
  - In most cases parent drug only.
  - In most BE studies racemic mixture (racemates) only when there is enantiomers

Contains Nonbinding Recommendations

Draft Guidance on Metformin Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Metformin Hydrochloride

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: The drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing.

2. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 1000 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comment above.

Analytes to measure: Metformin in plasma

Bioequivalence based on (90% CI): Metformin

Waiver request of in-vivo testing: 500 mg and 850 mg based on (i) acceptable bioequivalence studies on the 1000 mg strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Recommended Jul 2008

Contains Nonbinding Recommendations

Guidance on Clozapine[1]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Clozapine

Form/Route: Tablets/Oral

Recommended studies: 1 study

1. Type of study: Steady-state
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 100 mg
   Subjects: Patients who are receiving a stable daily dose of clozapine administered in equally divided doses at 12-hour intervals. Patients who are receiving multiples of 100 mg every 12 hours would be eligible to participate in the study of the 100 mg strength by continuing their established maintenance dose. FDA recommends that studies not be conducted using healthy subjects.
   Additional Comments: According to the randomization schedule, an equal number of patients would receive either the generic formulation (Treatment A) or the reference formulation (Treatment B) in the same dose as administered prior to the study every 12 hours for 10 days.

   Patients would then be switched to the other product for a second period of 10 days. No washout period is necessary between the two treatment periods. After the study is completed, patients could be continued on their current dose of clozapine using an approved clozapine product as prescribed by their clinicians

Analytes to measure (in appropriate biological fluid): Clozapine in plasma.

Bioequivalence based on (90% CI): Clozapine

Waiver request of in-vivo testing: 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12

[1] These recommendations were issued as a final guidance in June 2005 and moved to Individual Product Bioequivalence Recommendations in March 2011.

Finalized June 2005

LCK Pharmaceutical Consulting

Active ingredient: Lidocaine

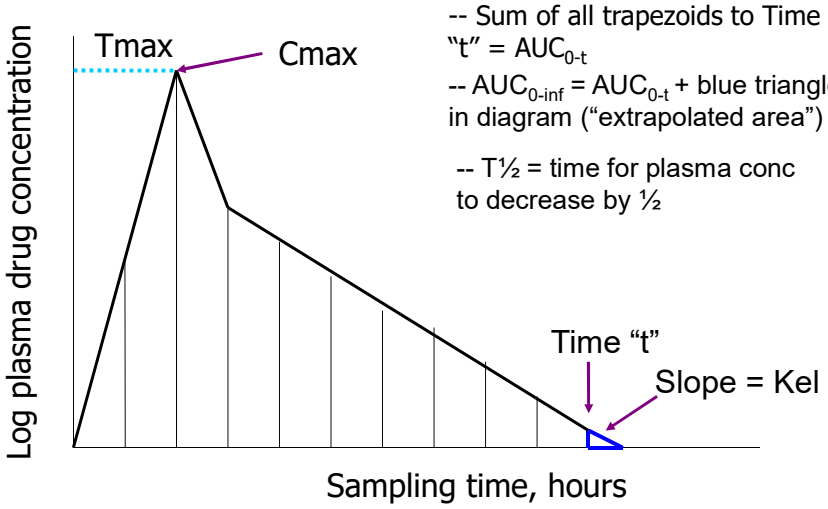
Form/Route: Patch/Topical

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, in vivo, using three topical patches
   Strength: 5%
   Subjects: Normal healthy males and females, general population.
   Additional Comments:
   - Apply three topical patches simultaneously over a 12-hour period.
   - You may use a smaller number of patches provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence assessment based on the 90% confidence interval criteria.
   - Please include a 24-hour post-dose sampling time in the bioequivalence study.
   - In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.

LCK Pharmaceutical Consulting

PHARMACOKINETIC…



-- Sum of all trapezoids to Time "t" = AUC_{0-t}

-- AUC_{0-inf} = AUC_{0-t} + blue triangle in diagram ("extrapolated area")

-- T½ = time for plasma conc to decrease by ½

SOME INTERNATIONAL CRITERIA

Regulatory Agency	90 % confidence interval on Log transformed data		
	C_{max} %	AUC_{0-t} %	$AUC_{0-\infty}$ %
U.S.A.	80-125	80-125	80-125
Europe & Australia	80-125	80-125	Not Applicable
Canada	Ratio must be between 80-125 Need to pass also on potency corrected data. Add-on studies may be allowed if intra- CV greater than expected	80-125	Not Applicable
South Africa	75-133	80-125	Not Applicable
Saudi Arabia	80-125	80-125	80-125
ASEAN	80-125	80-125	80-125
South Korea	80-125	80-125	80-125
Mexico	80-125	80-125	Not Applicable

PHARMACOKINETIC… BIO-WAIVERS

- Products marketed as
  - single strength or multiple strengths
- Do all strengths need to be studied for BE?
  - Acceptable in vivo BE must be established for one strength (generally the highest strength)
  - Dissolution testing on all strengths must be acceptable
  - Strengths must be proportionally similar to the bio-strength
- For safety reasons;
  - an in vivo study on a lower strength, and grant biowaiver(s) on higher strength(s)
    - Example: Terazosin Hydrochloride Tablets, 1, 2, 5, and 10 mg strength
    - Because of safety concerns, FDA requests fasting BE study on the 2 mg strength
    - biowaivers on 1, 5, and 10 mg strengths

PHARMACOKINETIC… BIO-WAIVERS BCS

- Highly soluble
  - An amount of drug comparable to the highest strength must be soluble in 250 mL of solution over wide pH range
- Highly permeable
  - Can be established by in vivo or in vitro methods
- Rapidly dissolving
  - In 0.1N HCl (pH 1.2), pH 4.5, and pH 6.8 buffers;
  - 900 mL, using paddle at 50 rpm or basket at 100 rpm
- Example: Levofloxacin tablets, 250, 500, and
- 750 mg
  - Solubility > 750 mg/250 mL
  - Oral bioavailability ≈ 99%
  - Dissolution is rapid at pH 1.2, 4.5, and 6.8
  - FDA designated the drug as BCS Class I and granted biowaiver

PHARMACOKINETIC… BIO-WAIVERS DESI

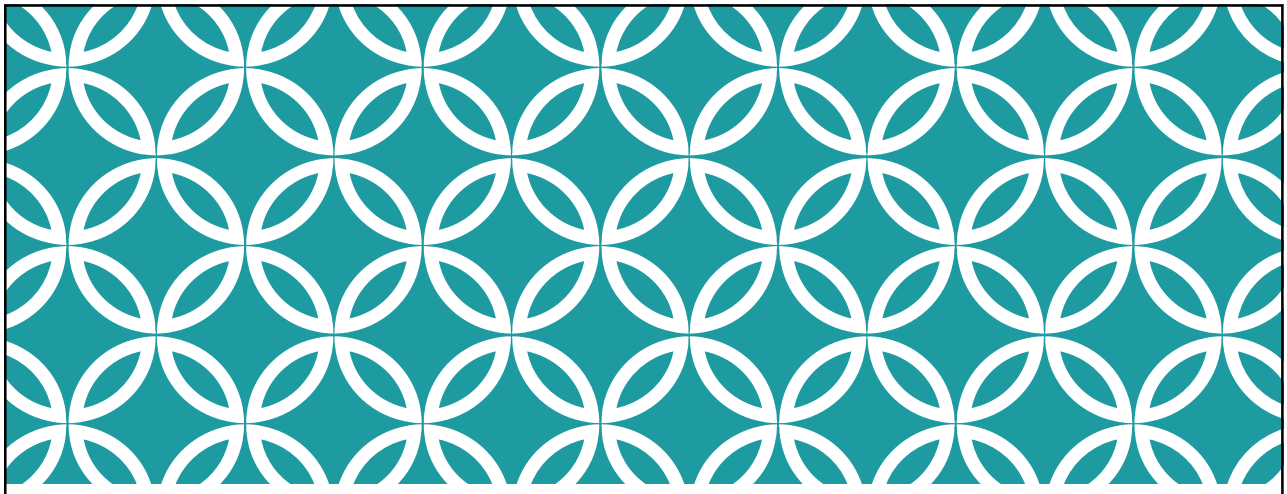
- Drug Efficacy Study Implementation (DESI) was conducted in the 1970s
- Panel of scientific experts conducted study
- In vivo BE studies can be waived for solid oral dosage forms that meet these criteria
  - Approved before 1962 in US
  - Determined to be efficacious by DESI panel
  - No BE problems
  - Dissolution data must be acceptable
- Example: Hydroxyzine Hydrochloride Tablets (meet all the above criteria)

IN VIVO BE PROBLEMS

- BE studies in vivo – small scale clinical trials! (12-36 subject)
- Lack of appropriate regulations
  - We have never inspected CROs conducting BE study
- Lack of ethical review/ review capacity
- Local industries may not have the experience and resources
- Lack of regulatory capacity
  - Lack of financial resources
  - Lack of adequately trained human resources
- Sever problems with CROs revealed by WHO inspections (in the framework of WHO prequalification programme)
  - Data fraud
  - Data quality, reliability etc

USEFUL LINKS

- Dissolution database: http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm
- Individual product BE recommendations database: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
  - **Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 1026]**
- FDA guidances: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
- Electronic Common Technical Document (eCTD) Basics: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm



THANK YOU
QUESTIONS