Palestinian National Authority
Ministry of Health

السـلطة الوطنيـة الفلسـطينية
وزارة الصحة

GENERAL GUIDELINES

FOR

IN VIVO BIOEQUIVALENCE STUDIES

February, 2010

Table of Contents

Table of Contents (continued) **Page**

I. Introduction

Generic pharmaceutical drug products must conform to the same standards, quality, safety and efficacy as originator comparator drug products so as to become therapeutically interchangeable with the originator drug.

In order to demonstrate interchangeability with the comparator drug a generic equivalent must go through bioequivalence testing in a pharmacokinetic clinical trial on a set number of human subjects. The therapeutic equivalency will be determined by measuring systemic plasma concentration of the generic drug at various intervals after dosing in comparison to the systemic plasma concentration of the comparator drug. Bioequivalence studies would thus provide indirect evidence of the efficacy and safety of the generic drug. To achieve that bioequivalence studies must follow a rigid set protocol and be subject to inspection to verify compliance to set standards on Good Clinical Practice for the clinical phase of the study and Good laboratory Practice for the bioanalytical phase.

The guidelines presented here were prepared by Dr. Ramzi M. Sansur, Consultant to the Ministry of Health. They are based on those set by the WHO, FDA, EMEA, ICH as well as those used by some of the countries in the region and others. The Guidelines have been reviewed and commented on by the Pharmaceutical Department of the Palestinian Ministry of Health as well as members of the Union of Palestinian Pharmaceutical Manufactures (UPPM). Their comments were evaluated and relevant ones incorporated into the current Guidelines.

II. Objectives of the Guidelines

The objectives of these guidelines are to provide guidance for those organizations involved in the conduct, analysis and evaluation of in vivo bioequivalence studies. Organizations conducting such studies fall into various categories:

i) Contract Research Organizations (CRO). A CRO is contracted by a sponsor to perform bioequivalence studies on its product. A CRO can perform clinical trials at accredited facilities including any that it owns or operates.

ii) Site Management Organizations (SMO). An SMO is contracted by a sponsor to perform some or all aspects of clinical studies. An SMO does not own or operate clinical or bioanalytical sites but contracts accredited facilities to do that. It supervises all aspects of the study and generates a report based on the results obtained.

iii) Research Management Organization (RMO). An RMO provides pharmaceutical and biotechnology industry clients and physician investigator clients with high quality research through a wide variety of services and the standardization of research.

The need to perform bioequivalence studies on generic products (local or imported) whether newly introduced into the market or have been marketed for a while has become evident. Bioequivalence studies give a high level of confidence to the medical community and to consumers that generic products are as therapeutically effective as comparator innovator drugs. Even if the drug has been on the market for a while there still is a need to perform bioequivalence studies. This issue is very important for insuring therapeutic equivalency and good marketability of safe and effective drugs. Bioequivalence studies also apply to changes a manufacturer performs on a certain formulation if the change is deemed by the MOH to possibly affect its bioavailability.

The guidelines presented here have been prepared in full harmony with existing international European, USA, WHO and other regional guidelines and are fully in line with those of ICH. The guidelines have been divided to cover the clinical trial and bioanalytical phases of bioequivalence studies.

III. Definition Of Terms

Bioavailability

Bioavailability is 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 into 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

Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Comparator Drug Product

A pharmaceutical product used as a reference in a clinical trial. It can be an innovator drug or one that has passed bioequivalence studies and has been approved for marketing. Many countries have a list of such products for use in bioequivalence studies.

Crossover Study Design

A term used in clinical trials where one half of the subjects are administered the test pharmaceutical product while the second half are administered the reference product. The situation is reversed after a washout period.

Fixed Combination Products

Are drugs that are composed of more than one therapeutic ingredient.

Generic Product

Is defined as a pharmaceutical product that can be interchangeably used in place of the innovator product having the same therapeutic efficacy. It is also termed as "alternative or interchangeable or multisource pharmaceutical product".

Innovator Drug Products

Innovator drugs are normally considered as a patented drug that have passed all required tests and have been authorized for marketing by the relevant authority. Such products also termed as a "reference products".

Multiple Dose Studies

A study design whereby subjects are given the drug at fixed intervals in order to reach steady state.

Parallel Study Design

An alternate clinical study design where one group of subjects is administered the test drug and the second group the reference drug. This design is applied to drugs with long half life where adequate wash period is fairly long.

Replicate and Non-Replicate Study Design

Replicate design is typically a four period design where the test drug product is administered twice to each subject in each period and the reference product twice in each period. Non-replicate design is the standard two-period crossover design for bioequivalence studies where each subject is administered the test product at one period and the reference product on the second.

IV. Bioequivalence Studies Required

Pharmaceutically equivalent multi-source products should demonstrate therapeutic equivalency to be deemed as interchangeable. These include the currently marketed drugs or others in the process of being marketed. Various test methods are used to assess equivalence. These include:

A) Bioequivalence studies in humans whereby the active drug substance or active moiety or one or more of its metabolites are measured in biological fluids such as plasma, blood or urine.
B) Pharmacodynamic studies in humans.
C) Clinical trials
D) In-Vitro studies as part of Biowaver.

Several factors are involved in accepting test procedures that document equivalence of two pharmaceutical products. Bioequivalence studies that demonstrate equivalency of two drug products in biological fluids such as plasma are preferred. If a certain drug does not produce concentrations in biological fluids that can be measured using existing analytical technologies then pharmacodynamic studies and clinical trials may be necessary to demonstrate equivalency. In-vitro studies may sometimes be used if there is enough evidence of in-vitro/in-vivo correlations.

A) Bioequivalence Studies in Humans

Bioequivalence studies utilize pharmacodynamic parameters in biological fluids such as blood, plasma, serum or urine to demonstrate the release of the active drug substance or moiety from the drug product into the systemic circulation as opposed to measuring it at the site of action which may not be possible. As a result bioequivalence studies based on clinical trials in humans compare in vivo behavior of a test multi-source pharmaceutical product with that of a reference product.

The design of bioequivalence studies are done under clinical trial conditions and involves the administration on the reference and test product to a group of volunteers on two separate occasions separated by a washout period to insure elimination of the drug prior to the next dosing. Blood or urine samples are collected prior to drug administration and at various intervals post administration. The samples are then assayed for the concentration of the active moiety or metabolite(s). The change in concentration of the drug substance or its metabolites over time is an estimate of drug release and absorption into the systemic circulation. The pharmacokinetic parameters are calculated for each subject using validated statistical methodologies to determine acceptability factors.

a. Ethical Principals

All studies involving human subject should be conducted in accordance with current versions of the Declaration of Helsinki. Trials must be approved beforehand by an Ethics Committee (EC) or an Institutional Review Board (IRB) according to the regulations set by the MOH. An Ethics Committee (IRB) should act in an independent way and should not be staffed by any member associated with the sponsor or principal investigator or the CRO unless invited to participate in the discussions and offer clarifications. All discussions, recommendations and decisions should be documented in the minutes of its meetings. The IRB should be given reasonable time to review research protocols and Informed Consent Forms (IFC). The IFC must be written in a

simple language making it understandable to the subjects both orally and written. No subject should be allowed to participate without filling or being helped to fill the IFC in accordance to Good Clinical Practice (GCP). The information in the IFC must make it clear that participation is voluntary and the subject has the right to withdraw from the study at any time without having to give a reason except if they wish to. In such cases the reasons given should be documented. For those who withdraw compensation should be paid *pro rata temporis*. Subjects should be informed about insurance and other procedures for compensation or treatment should he or she be injured or disabled.

Any institution performing a study may form its own internal ethics committee but their decisions are subject to review by the IRB. Review Boards are normally staffed by professionals such as physicians, Ph.D. level physical or biological scientists and professionals within the field of study. They may also include pharmacists, nurses, health professionals, lawyers and ethicists. The main aim is to insure the rights and welfare of human subjects participating in the study. The Review Boards have the right to approve, reject or request modifications of any clinical trial presented to it. All clinical studies must conform to Good Clinical Practice (GCP) as per ICH: Guideline for Good Clinical Practice E6 (R1), and related publications such as E8, which have been approved by the MOH.

b. Study Design

1. Pilot Study

A pilot study using smaller number of subjects may be carried out before proceeding with a comprehensive bioequivalence study. Such studies are designed to assess sample collection time intervals, variability in obtained results and help optimize analytical methodologies. Pilot studies apply more for modified release products. Pilot studies are also subject to approval by IRB. If the number of subjects used in the pilot study is sufficient and the study design is suitable the results obtained may be used to document bioequivalence of the tested product. This is especially true if the number of subjects that have completed the study does not fall below twelve, which is the minimal number of subjects for any bioequivalence study. This will also require approval of the relevant authorities.

2. Non-replicate Study Design

Such studies are the common practice for testing bioequivalence of orally administered drug products for both immediate release and modified dosage forms. They are usually a crossover carried over two periods.

3. Replicate Study Design

These are recommended for highly variable drug products where within-subject variability is ≥30%. Such studies allow for comparisons of within-subject variance for the test and reference

drug products and may shed more information about factors affecting formulation performance. In this type of study the use of average bioequivalence is used to determine equivalence of the test product.

4. Food-Effect Studies

F**o**od-effect studies are designed to assess comparable bioavailability of a test product as compared to the reference. Such studies are sometimes recommended for modified release dosage forms. The design approach is a single dose, 2-period, 2- treatment, 2- sequence cross over study. Food-effect studies are not common in bioequivalence studies unless recommended by the sponsor. Most bioequivalence studies are done on fasting subjects.

c. Drug Products

1. Immediate Release Products

Immediate-release orally administered solid dosage forms include tablets, capsules and suspensions. Bioequivalence study protocols are carried on fasting subjects in a 2- way, 2- period cross over design using a test product and a reference or comparator drug with the highest available strength.

2. Modified Release Products

These include enteric coated and extended release products and include tablets, capsules filled with specially coated spansules or pellets and suspensions with coated granules. To assess bioequivalence for such products two protocols are recommended.

i) A single dose, non-replicate fasting study using the highest strength.
ii) A food-effect, non-replicate study also using the highest strength.

For extended release drugs multiple-dose studies are generally not recommended, even in situations where nonlinear kinetics are present.

The purpose of in vivo for modified release dosage forms can be summarized as follows:

i) The test product meets the controlled- release claimed.
ii) To rule out the occurrence of dosage dumping at any stage.
iii) To test the rate and extent of absorption.
iv) To determine fluctuations in drug concentrations.
v) To evaluate dose proportionality

Some studies may require that the modified release product be compared with an immediate release formulation to determine rate and extent of absorption, fluctuations in drug concentration, inter-individual variability of pharmacokinetic parameters investigated , and dose proportionality to assess linear pharmacokinetic properties. Linear pharmacokinetic properties are intended to establish similarity in total dosage released between the modified release dosage form and that of the immediate release form

Depending on the claim of the manufacturer of the drug release profile (e.g. 8, 12 or 24 hours), the blood sampling may be extended to 24 hours.

Food effect studies are especially important if the drug is recommended, by the manufacturer, to be taken with or immediately after a meal.

d. Subjects

According to various official sources the minimum number of subject to participate in and successfully complete a bioequivalence study is 12. This has been based on statistical analysis of many studies performed over the years. However a study protocol should enroll a larger number of subjects in the event that some of the participants may withdraw before or during the study. Thus a figure of 18-24 enrolled subjects is sufficient to produce statistically valid bioequivalence results and can account for dropouts.

Subjects often referred as participants or volunteers should be healthy 18-50 years and capable of giving informed consent. Most studies use healthy male volunteers but this is not a rule unless the drug is intended for use by one sex. If the drug is used predominantly by the elderly then the study design should include as many subjects above 60 years of age as possible. Drugs with significant toxicological effects (such as cancer drugs) should be studied as part of a therapeutic regime for patients and are not part of this guideline

The organization or institution performing bioequivalence studies should have a pool of healthy volunteers that have passed all medical tests and were selected. This will help avoid any compromises in selecting volunteers in preparation of a study. All subjects should have filled the informed consent form and were made aware of all aspects of risk factors associated with the study.

Medical tests for volunteers include documenting medical history, physical examinations, routine blood chemistry and hematology tests, urinalysis and liver and kidney function tests. No prescription or over the counter drugs are allowed within 2 weeks of the study. The consumption of caffeine containing beverages, alcohol and xanthine containing foods or smoking is not permitted within 48 hours of the initiation of the study. Subjects must fast prior to the study and be offered meals 4 hours after the initiation of the study as set by the study protocols. Meals during the study must be standardized to minimize inter-subject variability. Water is normally given ad libitum.

e. Drug Dosage and Dosing

Test products used in bioequivalence studies should be from a lot produced under normal production condition clearly identified by its lot number, manufacture and expiration dates. A comparator reference drug of the same dosage form and strength is then chosen. The reference drug should have passed bioavailability tests to be considered.

Bioequivalence studies are done using the highest approved strength, unless otherwise approved by the IRB. No dose should exceed recommended dose as per the label or official drug compendia.

In single dose studies the test and reference products are administered to subjects according to a randomized pre-assigned sequence following a fasting period of at least 10 hours. Fasting is continued for at least 4 hours after dosing. Subjects are normally allowed to drink water at will and may be allowed physical activities according to the study design. Throughout the study period subjects are monitored for vital signs and adverse events are recorded.

f. Moieties to be Measured

In most bioequivalence studies the active drug ingredient is measured in body fluids and in some cases, especially for drugs are rapidly metabolized, the principal metabolite(s) is measured. Most guidelines prefer that the active ingredient be measured as it would give a better profile of the rate of absorption of the test drug and can detect changes in the performance of formulations.

The difficulty with testing metabolites is first and foremost their availability and their stability. In addition some metabolism may occur in the digestive tract prior to the absorption of the active drug substance.

g. Bioanalysis

Bioanalytical methods should be tested and validated before any bioequivalence is attempted. These methods must be robust in the sense of being reproducible with a high recovery rate and give accurate results. Scientific literature abounds with many practical and applicable methods. In addition there are international guidelines such as those of the FDA on method validation. All analytical methodologies must be documented in the study protocols presented to the IRB.

The bioanalytical part of the bioequivalence study should be conducted according to the principals of GLP at accredited institutions. The current guidelines presented here will require analytical labs to be GLP certified by relevant institutions or authorities.

Bioanalytical methods used must be tested and validated prior to and after the study so as to provide reliable data. Validity includes:

- Stability of the active drug substance or the tested moiety in plasma or other body fluids during the entire period of storage.
- Specificity
- Accuracy
- Precision
- Minimum detection limits
- Response function.

The validation of analytical techniques must be able to distinguish the active drug substance from its metabolites which might elute at the same time. It is for this reason and for confirmatory purposes that the trend has been moving towards using not only chromatographic techniques but also spectrometric techniques through the use of mass spectrometry (MS). MS helps resolve the identity of the analyte and can distinguish it from one or more of its metabolites.

Deviations from set bioanalytical procedures must be rationalized and explained in the study reports.

h. Collection of Biological Samples

Blood samples are collected at time zero and at various intervals post-dosing according to the study protocol. Sufficient number of samples is collected within the time intervals to cover early absorption, peak and total absorption and give a meaningful "*Area Under the Curve*" (*AUC*). The sampling period should cover 3-5 half lives of active drug ingredient. All blood samples should be properly labeled, processed to obtain plasma or serum, relabeled then frozen for further analysis. Normally plasma is frozen at -20^{o} C for short term storage or -70^{o} C for longer storage. Depending on the study protocol 18 samples are normally obtained per subject. The freezer in which the samples are stored should have a log of temperature vs. time for quality assurance purposes so as to confirm the integrity of the samples during the storage period. A backup electricity generator is required in case of a power shortage.

i. Pharmacokinetic Parameters

Concentration of active drug substance in plasma samples over time give a good estimate of the absorption and elimination of the reference and test drug for assessing bioequivalence. For single dose bioequivalence studies, the following pharmacokinetic parameters are evaluated:

$AUC_{0\rightarrow t}$	=	*Area under the curve from time 0 to last quantifiable concentration*
$AUC_{0\rightarrow \infty}$	=	*Area under the curve from time 0 to infinity.*
C_{max}	=	*Maximum concentration.*
T_{max}	=	*Time to maximum concentration.*
λ_z	=	*Terminal elimination rate constant.*

$T_{1/2}$ = *Terminal elimination half life.*

In multiple dose studies (steady-state studies) the following pharmacokinetic studies are examined:

$AUC_{0\rightarrow Tss}$ = *Area under the curve, from time 0 to dosing interval, over a dosing interval at steady state.*

C_{maxss} = *Maximum concentration at steady state*

C_{minss} = *Minimum concentration at steady state.*

C_{avgss} = *Average concentration at steady state.*

T_{maxss} = *Time to maximum concentration at steady state.*

% Swing = $100\ (C_{maxss} - C_{minss}) / Cminss$

% Fluctuation = $100\ (C_{maxss} - C_{minss}) / Cavgss$

C_{max}, C_{maxss}, C_{minss}, T_{max} *and* T_{maxss} are determined directly from the observed data. *AUC* is estimated by the conventional trapezoidal rule. In multiple dose studies, at least 3 consecutive C_{minss} should be measured to insure attainment of steady state.

Bioequivalence of different formulations of the same drug substance (active ingredient) comprises equivalence to the rate and extent of drug absorption. The area under the the concentration time curve ($AUC_{0\rightarrow\infty}$) generally serves as characteristic of the extent of absorption, while for fast- releasing conventional formulations the maximum concentration (C_{max}), and the time of its occurrence (T_{max}), may serve as characteristic of the rate of absorption.

In multiple steady-state dose studies the percent peak trough fluctuation (*% Fluctuation*) and the *AUC* over one steady state dose interval ($AUC_{0\rightarrow Tss}$) can be used as primary characteristic of rate and extent of absorption, respectively.

If urinary samples are used, cumulative excretion, excretion rate at collection intervals, maximum excretion rate and time to maximum excretion are the pharmacokinetic parameters that are determined.

There are validated statistic software available from various sources that may be used to enter all the data to calculate the above mentioned parameters. This will facilitate data manipulation in light of the large number of data obtained per study.

j. Pharmacokinetic Measures of Systemic Exposure

Pharmacokinetic direct and indirect measures referred to above could be limited in their ability to assess drug rate of absorption. The US- FDA recommends a change in focus to measures of systemic absorption. The direct and indirect measures will still be valid and can be used to measure bioavailability and bioequivalence. Systemic exposure measures reflect comparable rate and extent of absorption and would ensure comparable therapeutic effects of the test product. Exposure measures are defined as follows:

1. Early Exposure

Bioequivalence of orally administered drugs can be demonstrated by measurement of peak and total exposure. The clinical trial study design should take that into consideration by collecting two quantifiable samples before the expected peak time to allow for adequate estimation of the partial areas. The partial area thus can be truncated at the population median of T_{max} values for the reference formulation.

2. Peak Exposure

Peak exposure can be assessed from the peak drug concentration (C_{max}) obtained directly from the data without interpolation.

3. Total Exposure

This recommendation applies to single dose studies as such:

- Area under the plasma concentration-time curve from time zero to time t ($AUC_{0\rightarrow t}$), where t is the last time point with measurable concentration for individual formulation.
- Area under the plasma concentration-time curve from time zero to time infinity ($AUC_{0\rightarrow\infty}$), where $AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + C_t / \lambda_z$, where C_t is the last measurable drug concentration and λ_z is the terminal or elimination rate constant calculated according to an appropriate method as set in the study design. It is also recommended that that the terminal half life ($t_{1/2}$) of the drug be also reported

For steady-state studies, it is recommended that the area under the plasma concentration-time curve ($AUC_{0\text{-}tau}$) from time zero to time span between dosing intervals (*tau*) be measured.

k. Long-Half life Drugs

For long half-life oral dosage forms, a non-replicate, single dose, crossover study can be conducted with an adequate washout period. Alternately a parallel design can be used. For both protocols sample collection time should be sufficient to ensure completion of gastrointestinal

transit of the drug product and absorption of the active drug substance which would take approximately 2-3 days.

l. Statistical Analysis and Acceptance Criteria

1. General Aspects

The analysis of variance (ANOVA) tables should be presented with the study report and should include all relevant statistical tests of all effects in the model. The output from ANOVAs appropriate to the study design and its application during the clinical trial must be expressed with enough significant figures to permit further data manipulations. Pharmacokinetic parameters used for ANOVA include *AUC*, T_{max} and C_{max}.

The final study report should include all data gathered for all subjects that successfully completed the clinical trial. Dropouts and withdrawal subjects should be mentioned. Supplementary analysis may be carried out using selected points or excluded subjects provided this is justified. Exclusion of more that 5% of the subjects (as long as the total number of participants who have completed the full study is according to the study design ≥ 12), or more than 10% of the data for a single subject/formulation must be justified and could be rejected by the IRB.

2. Decision Rules

Pharmacokinetic parameters to be tested, procedure for testing and acceptance range should be clearly stated in the study protocol that will be submitted to the IRB. For average bioequivalence the following apply:

- *AUC-ratio*: The 90% confidence interval should lie within an acceptance interval of 0.8-1.25. In specific cases such as for narrow therapeutic range drugs the acceptance interval could be tightened. In rare cases a wider acceptance range may be permitted if it is based on sound clinical justification.
- C_{max} - ratio: The 90% confidence interval should lie within an acceptance interval of 0.8-1.25. In specific cases such as for narrow therapeutic range drugs the acceptance interval could be tightened. In other cases a wider interval may acceptable. The interval must be prospectively defined, for example 0.75-1.33 but should be justified.
- t_{max}: Statistical evaluation of t_{max} could be used if there is a clinically relevant claim for rapid release or signs of adverse effects. The non-parametric 90% confidence interval should lie within a clinically determined range.
- *Other parameters*: $AUC_{0\rightarrow Tss,}$ C_{maxss}, C_{minss}, C_{avgss}, *% swing and % fluctuation* should be analyzed statistically after logarithmic transformation with the 90% confidence interval being within the acceptance range of 80-125%.

m. Presentation of Data

Concentration of active drug substances in plasma and other biological fluids at each time point for each subject should be presented in its original scale. The same applies to all pharmacokinetic data derived from the study. The mean, standard deviation and coefficient of variation for each variable should be computed and tabulated in the final report.

Pharmacokinetic parameters for the reference drug (R) and the generic drug being tested (T) for each subjected should be displayed in parallel. This includes *AUC*, C_{max}, the difference (T-R), ratio (T/R) and log of ratio (log T/R or Ln T/R) between the test and reference values should also be presented side by side for each participant. For each participant the summary tables should indicate in which sequence the subject received the product (T/R or R/T). For the test and reference product, arithmetic mean, geometric means of the logs and standard deviation (SD) of the logs should also be calculated for the *AUC* and C_{max}. All means: arithmetic, geometric, means of the logs, SD, and coefficients of variation should also be included in the report. Log_{10} rather than Ln are acceptable as long as this is clearly stated and is uniform throughout the calculations.

The pharmacokinetic parameters (λ_z and $T_{1/2}$) should be calculated for each participant following administration of the test and reference formulations. All points used in the λ_z determination i.e. time intervals used for estimation of the elimination rate constant, should be documented for future verification.

Plasma concentration at each sampling time point should be evaluated statistically using ANOVA. Analysis of variance using ANOVA after logarithmic transformation of *AUC* and C_{max} data as well as untransformed T_{max} data should be presented in the report. The report should also include the ANOVA analysis, source of variation (formulations, periods, sequences and subjects within sequence), degrees of freedom, sum of squares, mean square, F-test and Probability of "F" (α) values.

Parametric and/ or non-parametric 90% confidence intervals for the mean pharmacokinetic parameters and the point estimates should be calculated and presented as tables in the report.

If the two one sided t-tests were used as the decision criteria then values of both the upper and lower limits of the calculated test statistics and the tabulated t-value should be provided in the report.

n. Individual and Population Bioequivalence

According to EMEA most bioequivalence studies are designed, so far, to evaluate average bioequivalence as experiences with individual and population bioequivalence is limited. As a result this guideline will not offer specific recommendations in this regard.

o. Waivers for In-Vivo Bioequivalence Clinical Studies

- Proof of bioequivalence is required for most formulations. There are, however, cases in which the MOH may exempt certain formulations from having to perform bioequivalence

clinical trials. These depend on the BCS classification being highly soluble and highly permeable drugs (BCS class I). Formulations that may not require BE studies include:

1. Paranterally administered formulations (intravenous, intramuscular, subcutaneous, intrathecal) in the form of solutions having the same active drug substances, same concentrations and same excipients as the reference formulation.
2. Orally administered formulations having the same active drug substances, same concentrations as the reference drug and being highly soluble and highly permeable defined as class I in the BCS classification (see below). In such cases the excipients, if different, should not affect gastrointestinal absorption or transit of the active substance. In-vitro dissolution profile at different conditions should be comparable (refer to the section on in-vitro dissolution under B: "Other Approaches to Assess Bioequivalence", below).
3. Powders or granules for reconstitution as solutions as long as they meet the conditions stated in [1] and [2] above.
4. Solutions for ophthalmic and otic use as long as they meet the criteria mentioned in [1] and [2] above.
5. Aqueous topical products meeting the criteria mentioned in [1] and [2] above.
6. Inhalation products and nasal sprays meeting the criteria mentioned in [1} and [2] above as long as the dosing devices, according to laboratory studies, delivers the same dose as the reference product and perform similarly.

B. Other Approaches to Assess Bioequivalence:

For non-oral dosage forms such as topical creams and ointments and others it is necessary to prove, through in-vitro studies that the test and reference formulations have similar behavior. Such tests are sometimes referred to in official compendia.

a) Pharmacodynamic Studies

Pharmacodynamic studies are used when quantitative analysis of the active drug substance(s) or its metabolites cannot be accurately measured in body fluids. Such studies will become necessary to establish efficacy and safety of some drug formulations such as some topical products not intended for systemic circulation. Such studies should adhere to the principals, rules and regulations of Good Clinical Practice (GCP). The following requirements must be followed to demonstrate equivalency through pharmacodynamic drug responses:

1. The measured pharmacological or therapeutic response should be relevant to the claim of efficacy and/or safety.
2. The methodology must be validated for precision, accuracy for the measured response and be specific and reproducible.
3. Investigation of the dose response correlations for the test and reference drug must be established. Maximal responses will make it difficult to distinguish formulations given in doses.
4. The response produced should be quantitatively measured in a double blind study and be recorded in an instrument-produced and recorded way on a repetitive basis to provide a

record of the pharmacodynamic events as a substitute for plasma concentrations. Where this is not possible recording on visual analogue scales may be used. If the study only provides qualitative results then special statistical analysis should be applied.

5. Prior screening of subjects will be needed to exclude non-responders from the study. The criteria used to make such a judgment must be included in the study design.
6. If a placebo effect is expected to occur then a third phase with placebo treatment should be added in the study protocol.
7. The underlying pathology and natural history of the medical condition must be considered in the study design in order to gain knowledge of base-line conditions and assess reproducibility.
8. A crossover design may be used where appropriate. Alternately a parallel design approach could be used.

Where continuous variables could be recorded, these can be presented in the area under the effect- time curve, the maximum response and the time when the maximum response occurred. Statistical considerations follow similar principals as bioequivalence studies. Correction for the potential non-linearity of the relationship between dose and the area under the time effect curve should be performed on the basis of the outcome of the dosed-ranging study as mentioned earlier. Acceptance criteria do not have tom, necessarily, follow those used in bioequivalence studies. This must be clearly indicated and validated in the study protocol.

b) Comparative Clinical Studies

Comparative clinical studies should follow the guidelines set by the MOH whereby the study design must follow all rules and regulations in effect, be approved by the IRB and the MOH, be performed at a pre-designated clinical facility having a GCP accreditation. Such studies are not recommended for testing solid dosage forms for bioequivalence or bioavailability studies as they are more designed to measure efficacy and safety of tested drugs rather than bioequivalence. They are relegated to drug products where then analysis of the active ingredients or active moieties are not possible in body fluids.

c) Comparative In Vitro Dissolution, Biowaver and BCS

Dissolution testing is the first approach towards providing information on the solubility and rate of dissolution of drug products especially of orally administered drugs. They are also useful in assessing batch-to- batch uniformity. The dissolution testing should be used for:

1) Process control and quality assurance.
2) To determine the behavior of a drug after post approval minor modifications of the formulation for assessing if further bioequivalence studies would be required. Such modifications include changes in formulation which includes the source of the active drug substance or any of the excipients or even changes in excipients, process of manufacture, site of manufacture or manufacturing equipment. In such cases approval of the MOH is needed.

In vitro studies can help establish an in vivo/in vitro correlation. This correlation can also serve as an indicator of the behavior of drug under in vivo real life conditions. In vitro comparative dissolution studies are also required for Biowaver application. Biowaver mostly apply to high solubility, high permeability API (active pharmaceutical ingredient) based on BCS Class I drugs. It may also apply to dose-proportional other strength formulations based on in vitro studies with the stipulation that the original formulation has previously passed BE studies.

Dissolution method development report for solid dosage forms should be performed on three batches and includes the following:

- The pH solubility profile of the active drug substance
- Dissolution profiles at different speeds (100-150 rpm for Apparatus I, and 50-100 rpm for Apparatus II).
- Dissolution profiles for all strengths of the drug in a minimum of three dissolution media (pH 1.2, 4.5 and 6.8) according to WHO regulations. For drugs with poor solubility surfactants may be added to the dissolution media to enhance solubility.
- Where applicable official compendia method should be used.

If the above conditions are met for Class I BCS API then the relevant authorities may grant a Biowaver for the particular preparation.

It should be noted here that Biowaver is part of BE studies and is intended to reduce overall costs on generic drugs that meet certain criteria of BCS.

V. Institutions Conducting Bioequivalence Studies

As mentioned earlier there are 4 categories of institutions that can perform BE studies. Most bioequivalence studies are performed by contract research organizations (CRO) which, for the most part, are privately owned. CROs may be owned and operated by the drug manufacturer or be privately owned independent companies or institutions including qualified universities. A CRO may own its own clinical and/or bioanalytical facilities or could contract others to do part or all the work. All facilities where the study is performed should have relevant health authority certification and where possible international accreditation.

A new category of institutions performing bioequivalence work are the site management organizations (SMO). These organizations do not own any facility but contract accredited clinical and bioanalytical labs to do the work but, normally, under the SMO's supervision. They write the study protocol, oversee the clinical work, do the statistical analysis or contract others to do it and write the report.

There is also another type of organization being a hybrid SMO/CRO organization. The differences among any of these organizations are the level of legal responsibilities they incur. SMOs have the least legal responsibilities as this is relegated to the institutions they subcontract to perform the study. For full fledged CROs the contract with the study sponsor must indicate the level of obligation and the legal responsibility and liability for the study.

Institutions conducting bioequivalence studies or parts of it must be legally registered, insured and comply with the rules and regulations set by the MOH. These regulations are in full harmony with those published by the ICH, WHO, FDA, EMEA and other national bodies. The purpose of these regulations is to guide institutions performing bioequivalence studies in a manner that protects the rights of the participants of the study and to insure integrity and validity of results. It also insures that institutions performing bioequivalence studies fully comply with GCP and GLP at accredited sites.

For further details refer to "Additional Guidance for Organizations Performing in Vivo Bioequivalence Studies" (WHO Technical Report Series No. 937, 2006).

VI. Documentation

During the conduct of bioequivalence studies the following documents must be maintained:

1) Clinical Data: All relevant data are required to be maintained as per GCP Guidelines.
2) Analytical Method Validation:

    a. System suitability test
    b. Linearity range
    c. Lowest detection limit
    d. Quality Control sample analysis
    e. Sample stability analysis
    f. Sample recovery percent

3) Analytical data for collected plasma samples:

    a. Raw Data
    b. Chromatograms and/or spectrograms
    c. Variation in assay results
    d. Instrument calibration

4) Copies of the final report

VII. Study Report

Bioequivalence study report must be written in compliance of ICH E3 guideline. The report must be signed by the principal investigator. It should include the name of the principal investigator(s), the site where the study was carried and the period in which it took place. If the site was audited by the responsible authority then the audit reports should be annexed.

The study report should indicate the reference drug substance chosen, its patented name, strength, dosage form, batch number, manufacturing and expiry dates, manufacturer, date and place and name of vendor where it was obtained. Reference drugs are best chosen from a list approved by the MOH or WHO.

For the test product the information submitted in the report should include certificate of analysis of various batches, especially the batch used in the study, manufacturing and expiry dates, batch size of the batch being tested and comparative dissolution profile as stated earlier in this guideline. A signed statement must be submitted by the sponsor, attesting that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for registration by the MOH.

All pharmacokinetic data and statistical analyses should be presented as mentioned above. All data including raw data, concentrations, pharmacokinetic parameters, randomization schemes must be kept in a soft format made available upon request.

VIII. Other Studies

a. Two-stage design

The use of two-stage study design for the demonstration of bioequivalence is acceptable provided statistical considerations are met. For example if a pilot bioequivalence study is attempted but bioequivalence has not been demonstrated with the acceptable limits of 0.8-1.25% then an additional group of subjects can be recruited and the results from both groups combined in the final analysis. As such the overall type I error of the experiment must be preserved. The results of the first pilot study should be treated as an interim analysis and the results of both analyses can be combined and adjusted accordingly. This will result in a different significance level having a probability higher than 90%. If this two-stage approach is taken it must be included in the study protocol and/or study report in conjunction with the adjusted significance levels used for each of the analyses.

b. Food Effect Studies

The following sections have been largely adapted from the USFDA/CDER "Guidance for Industry", December 2002 and are compatible with those of EMEA and ICH. They have been added with some detail due to the importance of this subject for drugs that are taken with meals and in particular modified release drugs.

I. Introduction

This guidance provides recommendations to sponsors and/or applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug This guidance applies to both immediate-release and modified-release drug products. This

guidance provides recommendations for food-effect BA and fed BE study designs, data analysis, and product labeling. It also provides information on when food-effect BA and fed BE studies should be performed.

II. Background

Food effect bioequivalence studies are usually conducted for drugs to demonstrate their bioequivalence to the reference drug under fed conditions to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions.

A. Potential Mechanisms of Food Effects on Bioavailability

Food can change the BA of a drug and can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including:

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase visceral blood flow
- Change luminal (gut) metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. It is recommended use of high-calorie and high-fat meals during food-effect BA and fed BE studies.

B. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances Biopharmaceutics Classification System (BCS Class I) because absorption of the drug substances in Class I are usually pH- and site-independent and thus insensitive to differences in

dissolution. However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, it is expected that food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in-vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

III. Recommendations

This section of the guidance provides recommendations on when food-effect BA and BE studies should be conducted. For post-approval changes in an approved immediate- or modified-release drug product that requires in vivo re-documentation of BE under fasting conditions, fed BE studies are generally unnecessary.

A. Immediate-Release Drug Products

It is recommended that a food-effect BA study be conducted for all new chemical entities during the drug investigation period. Food-effect BA studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect BA information should be available to design clinical safety and efficacy studies and to provide information for the clinical pharmacology and/or dosage and administration sections of product labels. If a sponsor makes changes in components, composition, and/or method of manufacture in the clinical trial formulation prior to approval, BE should be demonstrated between the to-be-marketed formulation and the clinical trial formulation.

The following are exceptions for a BE studies under fed conditions for immediate release products:

- When both test and reference products are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability, or
- When the dosage and administration section of the reference drug label states that the product should be taken only on an empty stomach, or
- When the reference drug label does not make statements about the effect of food on absorption or administration.

B. Modified-Release Drug Products

It is recommended that food-effect BA and fed BE studies be performed for all modified-release dosage forms. It is also recommended that a study comparing the BA under fasting and fed conditions be done for all orally administered modified-release drug products.

When changes occur in components, composition, and/or method of manufacture between the to-be-marketed formulation and the primary clinical trial material, the sponsor should consult with the MOH to determine if a new study would be needed.

IX. Study Considerations

This section provides general considerations for designing food effect BA and fed BE studies. A sponsor may propose alternative study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g. different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that co-administration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects.

A. General Design

It is recommended that a randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design for studying the effects of food on the BA of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal (fed condition) in the other period. It is recommended that a similar, two-treatment, two-period,

two-sequence crossover design for a fed BE study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies.

B. Subject Selection

Both food-effect BA and fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on BA to claim an absence of food effects, or to claim BE in a fed BE. A minimum of 12 subjects should complete the food-effect BA and fed BE studies.

C. Dosage Strength

In general, the highest strength of a drug product intended to be marketed should be tested in food-effect BA and fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For products with multiple strengths if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on comparative dissolution profile as detailed earlier.

D. Test Meal

It is recommended that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference. Sponsors can choose to conduct food-effect BA studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal as described above.

E. Administration

Fasted Treatments: Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

F. Sample Collection

For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. Consideration should be given to the possibility that co-administration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

X. Data Analysis and Labeling

Food-effect BA studies may be exploratory and descriptive, or a sponsor may want to use a food-effect BA study to make a label claim. The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- Total exposure, or area under the concentration-time curve ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$)
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant pharmacokinetic parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. An equivalence approach is

recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. Log-transformation of exposure measurements (*AUC* and C_{max}) prior to analysis is recommended. The 90 percent CI for the ratio of population geometric means between test and reference products should be provided for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}.

The effect of food on the absorption and BA of a drug product should be described in the "clinical pharmacology" section of the labeling. In addition, the "dosage and administration" section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance (i.e., whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns, or when there is no important change in systemic exposure but there is a possibility that the drug substance causes GI irritation when taken without food).

An absence of food effect on BA is not established if the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80-125 percent for either $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}t}$ when appropriate) or C_{max}. When the 90 percent CI fails to meet the limits of 80-125 percent, the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose-response (exposure-response) and/or pharmacokinetic-pharmacodynamic relationships of the drug under study. The clinical relevance of any difference in T_{max} and t_{lag} should also be indicated by the sponsor. The results of the food-effect BA study should be reported factually in the "clinical pharmacology" section of the labeling and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the "dosage and administration" section of the labeling.

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