## Guidelines for Bioequivalence Studies for Marketing Authorization of Generic Products

<table>
<thead>
<tr>
<th>Draft proposed by the committee (CEBS) on</th>
<th>28/05/2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoption by CAPA for release for feedback on</td>
<td>07/06/2009</td>
</tr>
<tr>
<td>Deadline for comments on</td>
<td>15/08/2009</td>
</tr>
<tr>
<td>Date of issue</td>
<td>14/1/2010</td>
</tr>
</tbody>
</table>

---

Committee for Evaluation of Bioequivalence Studies (CEBS)

---

Email: bioequivalence@eda.mohp.gov.eg  
Website: [http://eda.mohp.gov.eg](http://eda.mohp.gov.eg)
# Guidelines for Bioequivalence Studies
## for Marketing Authorization of Generic Products
### TABLE OF CONTENTS

**Objective**.............................................................................................................................................................. 1  
**Introduction**......................................................................................................................................................... 1  
**Glossary**............................................................................................................................................................... 1  
**Definitions**............................................................................................................................................................ 4  

**Pharmaceutical products exempted from equivalence studies**.................................................................5  
**Bioequivalence studies in humans**............................................................................................................ 6  
  
  Ethical considerations................................................................. 6  
  Study protocol........................................................................ 7  
  **Study design**........................................................................ 7  
    a) Single dose studies.......................................................... 7  
    b) Study design in patients................................................... 8  
    c) Studies on drugs with long elimination half lives..........8  
    d) Multiple dose studies...................................................... 9  
    e) Studies involving modified release products................. 9  
  Subjects..................................................................................... 10  
    a) Number of subjects....................................................... 10  
    b) Dropouts and withdrawals............................................ 10  
    c) Selection of subjects..................................................... 11  
    d) Monitoring the health of subjects during the study........12  
    e) Genetic phenotyping................................................. 12  
  Study standardization............................................................. 12  
  Pharmaceutical products under test....................................13  
  **Generic product**................................................................. 13  
  Reference Product................................................................. 13  
  Study conduct.......................................................................... 14  
  Parameters to be assessed................................................... 16  
  Studies of metabolites......................................................... 17  
  Measurement of Individual enantiomers............................17  
  Use of fed-state studies in bioequivalence determination.......17  
**Analytical test methods**...............................................................18  
**Statistical analysis**.................................................................................................................................19  
**Acceptance ranges**.................................................................................................................................20  
**Reporting of results**...............................................................................................................................21  
**Special considerations**.........................................................................................................................22  
  Fixed dose combination products .......................................22  
  Highly variable drugs...........................................................22  
**Pharmacodynamics studies**.............................................................................................................23  
**Clinical Bioequivalence Study**...........................................................................................................24  
**In vitro dissolution testing**..................................................................................................................25  
**Waiver of in vivo bioequivalence studies (Biowaiver)**.................................................................26  
**References**.................................................................................................................................30  
**Appendix I**.................................................................................................32  
**Appendix II**.................................................................................................34
**Objectives:**

These guidelines are intended to provide recommendations to sponsors and CROs on the requirements for approval of generic pharmaceutical products in Egypt. The guidance provides appropriate *in vivo* and *in vitro* requirements to assure interchangeability of the generic product without compromising the safety, quality and efficacy of the pharmaceutical product.

**Introduction:**

Generic pharmaceutical products need to conform to the same standards of quality, safety and efficacy of the originator's product. In addition they should be clinically interchangeable with equivalent marketed products.

This guidance is generally applicable to orally administered generic products, as well as to non-orally administered pharmaceutical products for which systemic exposure measures are suitable for documenting bioequivalence (e.g. transdermal delivery systems and certain parenteral, rectal and nasal pharmaceutical products). Other classes of products, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma, and products manufactured by biotechnology, are excluded from consideration in this document.

To ensure interchangeability, the generic product must be therapeutically equivalent to the reference product. Therapeutic equivalence can be assured when the generic product is both pharmaceutically equivalent/alternative and bioequivalent.

**Glossary**

**Bioavailability**

Bioavailability can be defined as the rate and extent to which the active pharmaceutical ingredient or active moiety is absorbed from a pharmaceutical dosage form and becomes available in the general circulation.

**Bioequivalence**

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of peak ($C_{\text{max}}$ and $t_{\text{max}}$) and area under the curve (AUC) after administration of the same molar dose under the same
conditions, are similar to such a degree that their effects can be expected to be essentially the same.

**Biopharmaceutics Classification System (BCS)**

The BCS is a system for classifying active pharmaceutical ingredients based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of the pharmaceutical product, the BCS takes into account three major factors that govern the rate and extent of drug absorption (exposure) from immediate-release oral solid dosage forms: dissolution, solubility, and intestinal permeability.

**Biowaiver**

The term biowaiver is applied to a regulatory drug approval process based on evidence of equivalence other than through *in vivo* equivalence testing.

**Reference product**

The reference product is a pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established.

**Dosage form**

The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

**Equivalence requirements**

*In vivo* and/or *in vitro* testing requirements for approval of a generic pharmaceutical product and marketing authorization.

**Equivalence test**

A test that determines the equivalence between the generic product and the reference product using *in vivo* and/or *in vitro* approaches.

**Fixed-dose combination (FDC)**

A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or brand. It may be administered as single-entity products given concurrently or as a finished pharmaceutical product.
Fixed-dose combination finished pharmaceutical product (FDC-FPP)
A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

Generic product
A pharmaceutically equivalent or pharmaceutically alternative product that may or may not be therapeutically equivalent. Generic pharmaceutical products that are therapeutically equivalent are interchangeable.

Innovator pharmaceutical product
Generally, the innovator pharmaceutical product is that which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy.

Interchangeable pharmaceutical product
An interchangeable pharmaceutical product is one which is therapeutically equivalent to a reference product and can be interchanged with the reference product in clinical practice.

In vitro equivalence test
An in vitro equivalence test is a dissolution test that includes comparison of the dissolution profile between the generic product and the reference product in three media: pH 1.2, pH 4.5 and pH 6.8.

In vitro quality control dissolution test
A dissolution test procedure identified in the pharmacopoeia, generally a one time point dissolution test for immediate-release products and a three or more time points dissolution test for modified release products.

Pharmaceutical alternatives
Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the reference product.
**Pharmaceutical equivalents**

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance.

**Therapeutic equivalents**

Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or *in vitro* studies.

**Definitions**

- $C_{\text{max}}$: maximum plasma concentration;
- $C_{\text{max,ss}}$: maximum plasma concentration at steady state;
- $C_{\text{min}}$: minimum plasma concentration;
- $C_{\text{min,ss}}$: minimum plasma concentration at steady state;
- $t_{\text{max}}$: time until $C_{\text{max}}$ is reached;
- $t_{\text{max,ss}}$: time until $C_{\text{max,ss}}$ is reached;
- $\text{AUC}_{0-t}$: area under the plasma concentration curve from administration to last observed concentration at time $t$;
- $\text{AUC}_{0-\infty}$: area under the plasma concentration curve extrapolated to infinite time;
- $\text{AUC}_t$: AUC during a dosage interval at steady state;
- Partial AUC: AUC truncated at the population median of $t_{\text{max}}$ values for the reference formulation;
- $t_{1/2}$: plasma concentration half-life;
- $C_{\text{av}}$: average steady state concentration ($\text{AUC}_t/\tau$);
- $k_{\text{el}}$: elimination rate constant;
- Fluctuation: $(C_{\text{max}} - C_{\text{min}})/C_{\text{av}}$;
- SPC: summary of Product Characteristics;
- SOP: standard operating procedures;
- ANOVA: analysis of variance;
- FDC: fixed dose combination;
- $F_s$: similarity factor;
- $R_t$: cumulative percentage of the drug dissolved at each of the selected time points of the reference product.
- $T_t$: cumulative percentage of the drug dissolved at each of the selected time points of the test product.
- ICH: International Conference on Harmonization;
- BCS: biopharmaceutics classification system.

**Methods to assess equivalence**

a) Comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient (APIs) and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic parameters, such as AUC and $C_{\text{max}}$ that are reflective of the systemic exposure;

b) Comparative pharmacodynamic studies in humans;

c) Comparative clinical trials; and

d) Comparative *in vitro* tests.

**Pharmaceutical products exempted from equivalence studies**

The following types of generic pharmaceutical products are considered to be equivalent without the need for further documentation. The generic product should contain the same APIs in the same molar concentration, and the applicant should demonstrate that the product contains the same or similar excipients in comparable concentrations as the reference product. Certain excipients may be different provided that it can be shown (if applicable) that the change(s) in the excipients would not affect the safety and/or efficacy of the pharmaceutical products:

a) Parenterally administered (e.g. intravenously, subcutaneously or intramuscularly) aqueous solutions;

b) Solutions for oral use (e.g. syrups, elixirs and tinctures). Critical review for the excipients known to affect absorption or stability of the APIs in GIT should be performed;

c) Powders for reconstitution as solution for parenteral or oral administration;

d) Pharmaceutical gases;

e) Otic or ophthalmic products prepared as aqueous solutions;

f) Topical products prepared as aqueous solutions; and
g) Aqueous solution for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device.

**Bioequivalence studies in humans**

*In vivo* documentation of equivalence is needed when there is a risk that possible difference in bioavailability may result in therapeutic inequivalence. Examples are listed below:

a) Oral immediate-release pharmaceutical products with systemic action when one or more of the following criteria apply:
   - Critical use medicines;
   - Narrow therapeutic range (efficacy/safety margins), steep dose-response curve;
   - Documented evidence for bioavailability problems or bioinequivalence related to the APIs or its formulations (unrelated to dissolution problems); and
   - Scientific evidence to suggest that polymorphs of APIs, the excipients and/or the pharmaceutical process used in manufacturing could affect bioequivalence.

b) Non-oral, non-parenteral pharmaceutical products designed to act systemically (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives).

c) Modified-release pharmaceutical products designed to act systemically.

d) Fixed-combination products with systemic action, where at least one of the APIs requires an *in vivo* study.

e) Non-solution pharmaceutical products, which are for non-systemic use (e.g. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption. In these cases, the equivalence is established through, e.g. comparative clinical or pharmacodynamic, dermatopharmacokinetic studies and/or *in vitro* studies. In certain cases, measurement of the concentration of the APIs may still be required for safety reasons, i.e. in order to assess unintended systemic absorption.

**Ethical considerations**

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki, including respect for persons, maximize benefits and do not be harmful, also according to Egyptian laws and regulations which ever represents the greater protection for subjects.
**Study protocol**

A bioequivalence study should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. The protocol should state the aim of the study and the procedures to be used, the reasons for proposing the study to be undertaken in humans, the nature and degree of any known risks, assessment methodology, criteria for acceptance of bioequivalence, the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. The investigator is responsible for ensuring that the protocol is strictly followed. Any change(s) required must be agreed on and signed by the investigator and sponsor, and included in the final report, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

The protocol and attachments/appendices should be scientifically and ethically appraised by Institutional Review Board (IRB) and or ethics committee in accordance with Egyptian drug regulatory authority guidelines.

A signed and dated study protocol together with the study report should be presented to the authorities in order to obtain the marketing authorization for the generic product.

**Study design**

In general, for a pharmacokinetic bioequivalence study involving a generic and a reference product, a two-period, single-dose, cross-over study in healthy volunteers will suffice. However, in certain circumstances, an alternative, well-established and statistically appropriate study design may be adopted.

**a) Single dose studies**

A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for pharmacokinetic bioequivalence studies. Each subject is given the generic and the reference product in randomized order. An adequate wash-out period should follow the administration of each product. The interval (wash-out period) between doses of each formulation should be long enough to permit the elimination of essentially all of the previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the terminal half-life of the APIs. This period should be extended if active metabolites with longer half-lives are produced and under some other circumstances as for example, if the elimination rate of the product has high variability between subjects. Just prior to...
administration of treatment during the second study period, blood samples are collected and assayed to determine the concentration of the APIs or metabolites. The minimum wash-out period should be at least seven days. The adequacy of the wash-out period can be estimated from the pre-dose concentration of the APIs and should be less than 5% of $C_{\text{max}}$. There is no need for blood samples to be collected for more than 72 hours. The study should be conducted under fasting conditions unless the intake of the product is recommended to be only in the fed state.

b) Study designs in patients

For APIs that are very potent or too toxic to administer in the usual dose to healthy volunteers (e.g. because of the potential for serious adverse events, or the trial necessitates a high dose) it is recommended that the study be conducted using the APIs at a lower strength. However, if the pharmacokinetics are not proportional or if the solubility of the APIs is an issue, it will not be appropriate to extrapolate the bioequivalence results of the studies at lower strength to those at higher strengths. For APIs that shows unacceptable pharmacological effects in healthy volunteers, a multiple dose, steady-state, cross-over study in patients or a parallel group design study in patients may be required. The alternative study design in patients should be justified by the sponsor who should attempt to recruit patients whose disease process is stable for the duration of the pharmacokinetic bioequivalence study.

c) Studies on drugs with long elimination half-lives

A single-dose cross-over pharmacokinetic bioequivalence study of an orally administered product with a long elimination half-life can be conducted provided an adequate wash-out period is used between administrations of the treatments. The interval between study days should be long enough to permit elimination of essentially all of the previous dose from the body. Ideally, the interval should not be less than five terminal elimination half-lives of the active compound or metabolite, if the latter is measured. Normally the interval between study days should not exceed 3 – 4 weeks. If the crossover study is problematic, a pharmacokinetic bioequivalence study with a parallel design may be more appropriate. For both crossover and parallel-design studies, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2–3 days) of the pharmaceutical product and absorption of the APIs. Blood sampling up to 72 hours following administration should
be carried out, unless shorter periods can be justified. The number of subjects should be derived from statistical calculations, but generally more subjects are needed for a parallel study design than for a cross-over study design.

d) Multiple –dose studies
In certain situations multiple-dose studies may be considered appropriate. Multiple-dose studies in patients are most useful in cases where the medicine being studied is considered to be too potent and/or too toxic to be administered to healthy volunteers, even in single doses. In this case, a multiple-dose cross-over study in patients may be performed without interrupting therapy. Evaluation of such studies can be based on either pharmacokinetic or pharmacodynamic end-points, although it is likely that using pharmacodynamic end-points would require a larger number of patients than pharmacokinetic end-points. The dosage regimen used in multiple-dose studies should follow the usual dosage recommendations.

Other situations in which multiple-dose studies may be appropriate are as follows:
- Drugs that exhibit non-linear kinetics at steady state (e.g. saturable metabolism, active secretion);
- Cases where the assay sensitivity is too low to adequately characterize the pharmacokinetic profile after a single dose;
- Extended-release dosage forms with a tendency to accumulation (in addition to a single-dose study).

In steady-state studies the wash-out of the last dose of the previous treatment can overlap with the approach to steady state of the second treatment, provided the approach period is sufficiently long (at least three times the terminal half-life). Appropriate dosage administration and sampling should be carried out to document for the attainment of a steady state.

e) Studies involving modified –release products
Modified-release products include extended-release products and delayed-release products. Extended-release products are variously known as controlled-release, prolonged-release and sustained-release products.

To establish the bioequivalence of modified-release products, a single-dose, non-replicate cross-over, fasting study comparing the highest strength of the generic and the reference product should be performed. Single dose studies are preferred to multiple-dose studies as
single-dose studies are considered to provide more sensitive measurements of the release of APIs from the pharmaceutical product into the systemic circulation. Multiple-dose studies may need to be considered (in addition to a single dose study) for extended-release dosage forms with a tendency to accumulate.

The reference product in this study should be a pharmaceutically equivalent modified-release product. The pharmacokinetic bioequivalence criteria for modified-release products are basically the same as for conventional-release dosage forms.

A concern with modified-release products is the possibility that food cause dumping. Therefore, a pharmacokinetic bioequivalence study under fed conditions is generally required, in addition to the study under fasting state, for orally administered modified-release pharmaceutical products. Omission of either the fed or fasting study should be justified by the applicant. A fed-state pharmacokinetic bioequivalence trial should be conducted after the administration of an appropriate standardized high fat meal at a specified time (usually not more than 30 minutes) before taking the medicine. The composition and caloric breakdown of the test meal should be provided in the study protocol and report refer to appendix I (Food - effect bioequivalence studies).

Subjects

a) Number of subjects

The number of subjects to be recruited for the study should be estimated by considering the standards that must be met. It should be calculated by appropriate statistical methods. The number of subjects recruited should always be justified by the sample-size calculation provided in the study protocol. A minimum of 24 subjects is required. (If otherwise, it should be justified).

b) Drop-outs and withdrawals

Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistic model and analysis, drop-outs generally should not be replaced. Reasons for withdrawal (e.g. adverse drug reaction or personal reasons) must be reported.

Sponsors who wish to replace drop-outs during the study or consider an add-on design should indicate this intention in the protocol. It is appropriate to recruit into the study more
subjects than the sample-size calculation requires. These subjects are designated as extras. The protocol should state whether samples from these extra subjects will be assayed if not required for statistical analysis.

If the bioequivalence study was performed with the appropriate number of subjects but bioequivalence cannot be demonstrated because of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study, provided this eventuality was anticipated and provided for in the study protocol. Combining data is acceptable only in the case that the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and SOPs, and must be given appropriate statistical treatment.

c) Selection of subjects

Pharmacokinetic bioequivalence studies should generally be performed with healthy volunteers. Clear criteria for inclusion and exclusion should be stated in the study protocol. If the pharmaceutical product is intended for use in both sexes, the sponsor may wish to include both males and females in the study. The risk to women will need to be considered on an individual basis, and if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study. Generally subjects should be between the ages of 18 and 55 years, and their weight should be within the normal range according to accepted life tables. The subjects should have no history of alcohol or drug abuse problems and should preferably be non-smokers.

The volunteers should be screened for their suitability using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual APIs being investigated, e.g. an electrocardiogram if the APIs has a cardiac effect. The ability of the volunteers to understand and comply with the study protocol has to be assessed. Subjects who are being or have previously been treated for any gastrointestinal problems, convulsive, depressive or hepatic disorders, and in whom there is
a risk of a re-occurrence during the study period, should be excluded. If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population) the selection criteria should be adjusted accordingly.

d) Monitoring the health of subjects during the study
During the study the health of volunteers should be monitored so that onset of side-effects, toxicity, or any intercurrent disease may be recorded, and appropriate measures taken. The incidence, severity, and duration of any adverse reactions and side-effects observed during the study must be reported. The probability that an adverse effect is drug-induced is to be judged by the investigator. Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study is conducted.

e) Genetic phenotyping
Phenotyping of subjects can be considered for studies of drugs that show phenotype linked metabolism and for which a parallel group design is to be used, because it allows fast and slow metabolizers to be evenly distributed in the two groups of subjects.
Phenotyping could also be important for safety reasons, determination of sampling times and wash-out periods in cross-over design studies.

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; and the 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. 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.
Medicines are usually given after an overnight fast of at least 10 hours, and participants are
allowed free access to water. On the morning of the study no water is allowed during the hour prior to drug administration. The dose should be taken with a standard volume of water (usually 150–250ml). Two hours after drug administration water is again permitted \textit{ad libitum}. A standard meal is usually provided four hours after drug administration. All meals should be standardized and the composition stated in the study protocol and report. Some medicines are normally given with food to reduce gastrointestinal side effects; incertain cases coadministration with food increases bioavailability of orally administered preparations. If the labelling states that the pharmaceutical product should be taken with food then a fed study should be used to assess bioequivalence. Fed state studies are also required in bioequivalence studies of modified release formulations. In these cases the objective is to select a meal that will challenge the robustness of the new generic formulation to prandial effects on bioavailability. The test meal selected should take account of local custom and diet and should be consumed within 20 minutes. The product should be administered according to the protocol and within 30 minutes after the meal has been eaten, as mentioned in appendix I (Food-effect bioequivalence studies).

\textbf{Pharmaceutical products under test:}

\textit{a) Generic product}

The generic pharmaceutical product used in the bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. Therefore, not only the composition and quality characteristics (including stability), but also the manufacturing methods (including equipment and procedures) should be the same as those to be used in the future routine production runs. Test products must be manufactured under GMP regulations. Batch-control results of the generic product, and the lot numbers and expiry dates of both generic and reference products should be stated. Samples should ideally be taken from production batches. It is recommended that potency and \textit{in vitro} dissolution characteristics of the generic and the reference pharmaceutical products be ascertained prior to performance of an equivalence study. Content of the APIs of the reference product should be close to the label claim, and the difference between two products should preferably be not more than \(\pm 5\%\).

\textit{b) Reference product}

The reference product should be selected based on the following options which are listed in order of preference.
(i) To choose the innovator product for which quality, safety and efficacy has been established if this product has been granted a marketing authorization in Egypt (“nationally authorized innovator”); or

(ii) To choose the WHO comparator (reference product) (for which marketing authorization has been granted, on the basis of quality, safety and efficacy) (“WHO comparator product”). The primary manufacturing site is indicated in the WHO comparator list, and the comparator (reference) is to be purchased in that country, or

(iii) To choose the innovator product for which a marketing authorization has been granted in a well-regulated country (ICH or associated country) on the basis of quality, safety and efficacy (“ICH et al. innovator”) and which is to be purchased from that market; or

(iv) In the case that no innovator product can be identified within the context of (i), (ii)&(iii) above, the choice of the reference must be made carefully and must be comprehensively justified by the applicant. The most important selection criteria in order of preference are:

- approval in ICH- and associated countries;
- “prequalified” by WHO;
- extensive documented use in clinical trials reported in peer-reviewed scientific journals; and
- long and unproblematic period of postmarket surveillance (“well selected reference”).

Additionally, “well selected reference” must conform to compendial quality standards, where these exist. The choice of reference product should be justified by the applicant. The country of origin of the reference product should be reported together with lot number and expiry date.

**Study conduct**

**a) Selection of dose**

In bioequivalence studies the molar equivalent dose of generic and reference product must be used.

Generally the marketed strength with the greatest sensitivity to bioequivalence assessment should be administered as a single unit. This will usually be the highest marketed strength. A higher dose (i.e. more than one dosage unit) may be employed when analytical difficulties exist. In this case the total single dose should not exceed the maximal daily dose of the dosage regimen. Alternatively, the application of area under the curve (AUC)
truncated to 3X median \( t_{\text{max}} \) of the reference formulation would avoid problems of lack of assay sensitivity in many cases. In certain cases a study performed with a lower strength can be considered acceptable if this lower strength is chosen for reasons of safety.

b) Sampling times

Blood samples should be taken at a frequency sufficient for assessing \( C_{\text{max}} \), AUC and other parameters. Sampling points should include a pre-dose sample, at least 2 points before \( C_{\text{max}} \), 2 points around \( C_{\text{max}} \) and 3–4 points during the elimination phase. Consequently at least seven sampling points will be necessary for estimation of the required pharmacokinetic parameters. For most medicines the number of samples necessary will be higher to compensate for between-subject differences in absorption and elimination rate and thus enable accurate determination of the maximum concentration of the APIs in the blood (\( C_{\text{max}} \)) and terminal elimination rate constant in all subjects. Generally, sampling should continue for long enough to ensure that 80% of the AUC\(_{0-\infty}\) can be accrued, but it is not necessary to sample for more than 72 hours. The exact duration of sample collection depends on the nature of the APIs and the input function from the administered dosage form.

In certain cases the use of partial (truncated) AUC could be used instead of the area extrapolated to infinity. For immediate-release formulations it is unnecessary to take blood samples beyond four times \( t_{\text{max}} \). This approach is of great value for products of APIs with a long \( t_{1/2} \) and in cases where low concentration occur in the terminal portion of the plasma concentration versus time curve, which may not be quantifiable by means of an adequately validated, sensitive analytical method.

c) Sample fluids and their collection

Under normal circumstances blood should be the biological fluid sampled to measure the concentrations of the APIs. In most cases the APIs or its metabolites are measured in serum or plasma. If the APIs is excreted predominantly unchanged in the urine, urine can be sampled. The volume of each sample must be measured at the study centre, where possible immediately after collection, and included in the report. The number of samples should be sufficient to allow the estimation of pharmacokinetic parameters. However, in most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the \( t_{\text{max}} \) and the maximum concentration.
Blood samples should be processed and stored under conditions that have been shown not to cause degradation of the analytes. This can be proven by analyzing duplicate quality control samples during the analytical period. Quality control samples must be prepared in the fluid of interest (e.g. plasma), including concentrations at least at the low, middle and high segments of the calibration range. The quality control samples must be stored with the study samples and analyzed with each set of study samples for each analytical run. The sample collection methodology must be specified in the study protocol.

**Parameters to be assessed**

a) For single-dose studies, the following parameters should be measured or calculated:

- Area under the plasma / serum / blood concentration–time curve from time zero to time t(AUC\(_{0-t}\)), where t is the last sampling time point with a measurable concentration of the APIs in the individual formulation tested. The method of calculating AUC-values should be specified. In general AUC should be calculated using the linear/log trapezoidal integration method. The exclusive use compartmental-based parameters is not recommended.
- \(C_{\text{max}}\) is the maximum or peak concentration observed representing peak exposure of APIs (or metabolite) in plasma, serum or whole blood. AUC\(_{0-t}\) and \(C_{\text{max}}\) are considered to be the most relevant parameters for assessment of bioequivalence.

In addition it is recommended that the following parameters be estimated:

- Area under the plasma/serum/blood concentration–time curve from time zero to time infinity (AUC\(_{0-\infty}\)) representing total exposure, where AUC\(_{0-\infty}\) = AUC\(_{0-t}\) + C\(_{\text{last}}\)/\(k_{\text{el}}\); C\(_{\text{last}}\) is the last measurable drug concentration and \(k_{\text{el}}\) is the elimination rate constant calculated according to an appropriate method;
- \(t_{\text{max}}\) is the time after administration of the drug at which \(C_{\text{max}}\) is observed.

For additional information, the following elimination parameters can be calculated:

- \(t_{1/2}\) is the plasma, serum or whole blood half-life.
- \(k_{\text{el}}\) is the elimination rate constant.

b) For steady-state studies the following parameters can be calculated:

- AUC\(_{\tau}\) is AUC over one dosing interval (\(\tau\)) at steady-state;
- \(C_{\text{max,ss}}\)
- \(C_{\text{min,ss}}\) is concentration at the end of a dosing interval;
- Peak-trough fluctuation is the percentage difference between \(C_{\text{max}}\) and \(C_{\text{min}}/C_{\text{average,ss}}.\)
c) When urine samples are used, cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_max.

**Studies of metabolites**

Generally, evaluation of pharmacokinetic bioequivalence will be based upon the measured concentrations of the parent drug released from the dosage form rather than the metabolite.

It is important to state a priority in the study protocol which chemical entities (pro-drug, drug (APIs) or metabolite) will be analyzed in the samples.

In some situations it may be necessary to measure metabolite concentrations rather than those of the parent drug for instance:

- The measurement of concentrations of therapeutically active metabolite is acceptable if the substance studied is a pro-drug.
- Measurement of a metabolite may be preferred when concentrations of the parent drug are too low to allow reliable analytical measurement in blood, plasma or serum for an adequate length of time, or when the parent compound is unstable in the biological matrix.

When measuring the active metabolites, wash-out period and sampling times may need to be adjusted to enable adequate characterization of the pharmacokinetic profile of the metabolite.

**Measurement of individual enantiomers**

A non-stereoselective assay is currently acceptable for most pharmacokinetic bioequivalence studies. When the enantiomers have very different pharmacological or metabolic profiles, assays that distinguish between the enantiomers of a chiral APIs may be appropriate. Stereoselective assay is also preferred when systemic availability of different enantiomers is demonstrated to be non linear.

**Use of fed-state studies in bioequivalence determination**

a) Immediate-release formulations

Fasted-state studies are generally preferred. When the product is known to cause gastrointestinal disturbances if given to subjects in the fasted state, or if labelling restricts administration to subjects in the fed state, then the fed-state pharmacokinetic bioequivalence study becomes the preferred approach. The composition of the meal may depend on local diet and customs.
b) Modified-release formulations

Food-effect studies are necessary for all generic modified-release formulations to ensure the absence of “dose dumping” which results in a premature and abrupt rise in the plasma concentration time profile. A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should also take local diet and custom into consideration.

Analytical test methods

All analytical test methods used to determine the active compound and/or its biotransformation product in the biological fluid must be well characterized, fully validated and documented. The following are important recommendations for the conduct of analysis of biological samples in a pharmacokinetic study:

• Validation comprises pre-study and within-study phases. During the pre-study phase stability of the stock solution and spiked samples in the biological matrix, specificity, sensitivity, accuracy, precision and reproducibility should be provided. Within-study validation proves the stability of samples collected during a clinical trial under storage conditions and confirms the accuracy and precision of the determinations.

• Validation must cover the intended use of the assay.

• The calibration range must be appropriate to the study samples. A calibration curve should be prepared in the same biological matrix as will be used for the samples in the intended study by spiking the matrix with known concentrations of the analyte. A calibration curve should consist of a blank sample, a zero sample, and 6-8 non-zero samples covering the expected range. Concentrations of standards should be chosen on the basis of the concentration range expected in a particular study.

• If an assay is to be used at different sites, it must be validated at each site, and cross-site comparability established.

• An assay which is not in regular use requires sufficient revalidation to show that it still performs according to the original validated test procedures. The revalidation study must be documented, usually as an appendix to the study report.

• Within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged.
• If different studies are to be compared and the samples from the different studies have been assayed by different methods, and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.

• Spiked quality control samples at a minimum of three different concentrations in duplicate should be used for accepting or rejecting the analytical run.

• All the samples from one subject (all periods) should be analyzed in the same analytical run, if possible.

Validation procedures, methodology and acceptance criteria should be specified in the analytical protocol, and/or the SOPs. All experiments used to support claims or draw conclusions about the validity of the method should be described in a report (method validation report). Any modification of the method during the analysis of study samples will require adequate revalidation. The results of study sample determination should be given in the analytical report together with calibration and quality control sample results, repeat analysis (if any), and a representative number of sample chromatograms.

**Statistical analysis**

Statistical analysis of the bioequivalence trial should demonstrate that a clinically significant difference in bioavailability between the generic product and the reference product unlikely. The statistical procedures should be specified in the protocol before the data collection starts. The statistical method for testing pharmacokinetic bioequivalence is based upon the determination of the 90% confidence interval around the ratio of the log-transformed population means (generic/reference) for the pharmacokinetic parameters under consideration and by carrying out two one-sided tests at the 5% level of significance. To establish pharmacokinetic bioequivalence, the calculated confidence interval should fall within a preset bioequivalence limit. The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e. leading to the same decision whether the generic formulation is compared to the reference product or the reference product to the generic formulation).

All concentration-dependent pharmacokinetic parameters (e.g. AUC and \(C_{\text{max}}\)) should be log-transformed using either common logarithms to the base 10 or natural logarithms. The choice of common or natural logs should be consistent and should be stated in the study report. Logarithmically transformed, concentration-dependent pharmacokinetic parameters should be
analyzed using analysis of variance (ANOVA). Usually the ANOVA model includes the formulation, period, sequence or carry-over and subject factors.

Parametric methods, i.e. those based on normal distribution theory, are recommended for the analysis of log-transformed bioequivalence measures. The general approach is to construct a 90% confidence interval for the quantity $\mu T - \mu R$ and to reach a conclusion of pharmacokinetic equivalence if this confidence interval is within the stated limits. The nature of parametric confidence intervals means that this is equivalent to carrying out two one-sided tests of the hypothesis at the 5% level of significance. The antilogs of the confidence limits obtained constitute the 90% confidence interval for the ratio of the geometric means between the generic and reference products.

The same procedure should be used for analyzing parameters from steady state trials or cumulative urinary recovery, if required.

For $t_{\text{max}}$ descriptive statistics should be given. If $t_{\text{max}}$ is to be subjected to a statistical analysis this should be based on non-parametric methods and should be applied to untransformed data. A sufficient number of samples around predicted maximal concentrations should have been taken to improve the accuracy of the $t_{\text{max}}$ estimate. For parameters describing the elimination phase ($t_{1/2}$) only descriptive statistics should be given.

Methods for identifying and handling of possible outlier data should be specified in the protocol. Medical or pharmacokinetic explanations for such observations should be sought and discussed. As outliers may be indicative of product failure, post hoc deletion of outlier values is generally discouraged. An approach to dealing with data containing outliers is to apply distribution-free (non-parametric), statistical methods.

If the distribution of log-transformed data is not normal, non-parametric statistical methods can be considered. The justification of the intent to use non-parametric statistical methods should be included a priori in the protocol.

Acceptance ranges

*Area under the curve-ratio*

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80–1.25. If the therapeutic range is particularly narrow, the acceptance range may need to be reduced based on clinical justification. A larger acceptance range may be acceptable in exceptional cases if justified clinically.
**C_{\text{max}}$$-\text{ratio}$$**

In general the acceptance limit 0.80–1.25 should be applied to the \( C_{\text{max}} \)-ratio. However, in certain cases a wider acceptance range (e.g. 0.75–1.33) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.

**t_{\text{max}}$$-\text{difference}$$**

Statistical evaluation of \( t_{\text{max}} \) makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

For other pharmacokinetic parameters the same considerations as outlined above apply.

**Reporting of results**

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with good clinical practice rules. The responsible investigator(s) should sign their respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated. The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the test product(s) should be given. Results of *in vitro* dissolution tests should be provided. In addition, the applicant should submit a signed statement confirming that the test product is identical to the pharmaceutical product which is submitted for registration. The bioanalytical validation report should be attached. The bioanalytical report should include the data on calibrations and quality control samples. A representative number of chromatograms or other raw data should be included covering the whole calibration range, quality control samples and specimens from the clinical trial.

All results should be presented clearly. All concentrations measured in each subject and the sampling time should be tabulated for each formulation. Tabulated results showing APIs concentration analysis according to analytical run (including runs excluded from further calculations, including all calibration standards and quality control samples from the respective run) should also be presented. The tabulated results should present the date of run, subject, study period, product administered (generic or reference) and time elapsed between drug
application and blood sampling in a clear format. The procedure for calculating the parameters used (e.g. AUC) from the raw data should be stated. Any deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual blood concentration/time curves should be plotted on a linear/linear and log/linear scale. All individual data and results should be given, including information on those subjects who dropped out. The drop-outs and/or withdrawn subjects should be reported and accounted for.

Results of all measured and calculated pharmacokinetic parameters should be tabulated for each subject–formulation combination together with descriptive statistics. The statistical report should be sufficiently detailed to enable the statistical analysis to be repeated if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

Special considerations

Fixed-dose combination products

If the pharmacokinetic bioequivalence of fixed-dose combination (FDC) products is assessed by in vivo studies the study design should follow the same general principles as described in previous sections. The generic FDC product should be compared with the pharmaceutically equivalent reference FDC product. In certain cases (e.g. when no reference FDC product is available on the market) separate products administered in free combination can be used as a reference. Sampling times should be chosen to enable the pharmacokinetic parameters of all APIs to be adequately assessed. The bioanalytical method should be validated on respect to all compounds measured. Statistical analysis should be performed with pharmacokinetic data collected on all active ingredients; the 90% confidence intervals of test/reference ratio of all active ingredients should be within acceptance limits.

Highly variable drugs

A “highly variable drug” has been defined as an APIs with a within-subject variability of ≥ 30% in terms of the ANOVA-CV. Moreover “highly variable drugs” are generally safe drugs with shallow dose–response curves.

To overcome the problems of proving the bioequivalence of medicinal products containing "highly variable drugs":
i) Large number of subjects must be enrolled in the studies to achieve adequate statistical power, or

ii) Broadened bioequivalence limits are used (e.g. 0.75-1.33 instead of 0.8-1.25) provided there is adequate justification; taken into consideration the therapeutic category of the drug.

**Pharmacodynamic studies**

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products. Pharmacodynamic bioequivalence studies may become necessary if quantitative analysis of the APIs and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity:

Pharmacodynamic bioequivalence studies may be appropriate for pharmaceutical products administered topically and for inhalation dosage forms. If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP must be followed.

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by measuring pharmacodynamic drug responses.

- The response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the test product nor the reference product should produce a maximal response in the course of the study, since it may be impossible to detect differences between formulations given in doses which give maximum or near-maximum effects. Investigation of dose–response relationships may be a necessary part of the design.
- The response should be measured quantitatively, preferably under double-blind conditions, and be recordable by an instrument that produces and records the results of repeated measurements to provide a record of the pharmacodynamic events, which are substitutes for measurements of plasma concentrations. Where such measurements are not possible, recordings on visual analogue scales may be used. Where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.
- Participants should be screened prior to the study to exclude non-responders. The criteria by which responders are distinguished from non-responders must be stated in the protocol.
- In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by a priori consideration of the potential placebo effect in the
study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.

- The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of baseline conditions.
- A cross-over design can be used. Where this is not appropriate, a parallel group study design should be chosen.

The selection basis for the generic and reference products should be the same as described under pharmacokinetic bioequivalence studies.

In studies in which continuous variables can be recorded, the time-course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations are measured, and parameters can be derived which describe the area under the effect–time curve, the maximum response and the time at which the maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle the same as those outlined for the analysis of pharmacokinetic bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect–time curve should be performed on the basis of the outcome of the dose-ranging study. It should be noted that the acceptance range as applied for bioequivalence assessment may not be appropriate and should be justified on a case-by-case basis and defined in the protocol.

**Clinical Bioequivalence Study**

On conducting a clinical bioequivalence study the following should be defined in the protocol:

- The target parameters that usually represent relevant clinical end-points from which the onset, if applicable and relevant, and intensity of the response are to be derived.
- The number of patients which will depend on the variability of the target parameters and the acceptance range and is usually much higher than the number of subjects needed in pharmacokinetic bioequivalence studies to achieve adequate statistical power.
- The size of the acceptance range has to be defined case by case, taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter.
- The size of the acceptance range in clinical trials should be set individually according to the therapeutic class and indication(s).
- A one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence
intervals can be derived from either parametric or non-parametric methods.

- Where appropriate, a placebo leg should be included in the design.
- In some cases it is relevant to include safety end-points in the final comparative assessments.
- The selection basis for the generic and reference products should be the same for in vivo equivalence studies.

**In vitro Dissolution Testing**

*In vitro* dissolution studies should be based on the generation of comparative dissolution profiles rather than a single-point dissolution test. The dissolution profile of the two products should be measured under the same test conditions, using either the paddle method at 75 rpm or the basket method at 100 rpm using buffers of pH 1.2, 4.5 and 6.8 as dissolution media at 37°C. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product completely, e.g. at 10, 15, 20, 30, 45 and 60 minutes. A minimum of 12 dosage units of each product should be evaluated.

The dissolution profiles of the generic and reference products can be compared using a similarity factor (f<sub>2</sub>). Data with less than 20% variance at the first time-point and less than 10% variance at subsequent time-points can be used for the f<sub>2</sub> calculation, noting that a maximum of one time-point should be considered after 85% dissolution of the reference product has been reached. A minimum of three time-points (zero excluded) is required for the calculation of f<sub>2</sub>. An f<sub>2</sub> value of 50 or greater (50–100) reflects sameness or equivalence of the two curves and thus equivalence of the in vitro performance of the two products. The similarity factor f<sub>2</sub> is to be computed using the equation:

\[
 f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} n(R_t - T_t)^2] -0.5 \cdot 100\}
\]

Where R<sub>t</sub> and T<sub>t</sub> are the cumulative percentage of the drug dissolved at each of the selected n time-points of the reference and generic (test) product respectively.

If the reference and generic products are very rapidly dissolving, i.e. at least 85% dissolution in 15 minutes or less, in all three media, using the recommended test method, a profile comparison is not necessary.

Other appropriate statistical methods can also be used for comparison of dissolution profiles, provided that the same criterion is used for acceptance (maximum 10% difference between the profiles).

In case of performing the in vivo bioequivalence (biowaiver is not applicable), the dissolution test
required should be a comparative dissolution test on 12 dosage units for each strength of the test and reference product. Samples of the dissolution media at time intervals should be withdrawn and analyzed (not less than 6 points). A suitable dissolution medium should be used based on pharmacopeal requirements or the literature. Samples should be analyzed using a validated method of analysis. If the method is official or reported, only the linearity item is required for validation of the method.

**Waiver of in vivo bioequivalence studies (Biowaiver).**

1. **Biowaiver based on the biopharmaceutics classification systems (BCS)**

BCS-based biowaiver are applicable for an immediate release drug product if:

a) The drug substance has been proven to exhibit high solubility and complete absorption (BCS-Class I). The highest single dose administered as immediate release formulation(s) should completely dissolve in ~250ml of buffers of pH 1.2, 4.5 and 6.8. A minimum of 3 replicate determinations at each pH conditions is recommended. Complete drug absorption should be justified based on reliable investigations in humans (extent of absorption ≥ 85%). Data from absolute bioavailability or mass balance studies could be used to support this plan.

b) Very rapid (> 85% within 15min) in vitro dissolution characteristics of the generic and reference products have been demonstrated. A paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in volume of 900 ml or less in media of pH 1.2, 4.5 or 6.8 is used.

c) Excipients are not suspect of having any relevant impact on bioavailability.

BCS-based biowaiver are also applicable for an immediate release drug product if:

a) The drug substance has been proven to exhibit high solubility and limited absorption where extent of absorption is less than 85% (BCS-Class III).

b) Very rapid (>85% within 15 min) in vitro dissolution of the generic and reference products have been demonstrated as previously mentioned.

c) Excipients are qualitatively the same and quantitatively very similar.

Biowaiver can be extended to BCS Class II weak acids, if the APIs has a dose: solubility ratio of 250ml or less at pH 6.8 and the generic product is rapidly dissolving (no less than 85% in pH 6.8 in 30minutes) and its dissolution profile is similar to that of the reference product at pH 1.2, 4.5 and 6.8. The excipients should additionally be critically evaluated in terms of type and amounts, e.g. of surfactants, in the formulation. Furthur, if the C\text{max} is critical to the therapeutic efficacy of
the APIs, the risk of reaching an inappropriate biowaiver decision is existing and unacceptable.

Biowaiver may be applicable when the active substance in generic and reference products are identical or belong both to BCS -Class I, in case of different salts, However, biowaiver may not be applicable when the generic product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference product. Also the drug substance should not belong to the group of narrow therapeutic range drugs.

d) Evidence that each excipient present in the generic product is well established and does not affect gastrointestinal motility or other processes affecting absorption, can be documented using the following information:

i) The excipient is present in the reference product, or the excipient is present in a number of other products which contain the same APIs as the generic drug product and which have marketing authorizations in countries participating in ICH or associated countries; and

ii) The excipient is present in the generic product in an amount similar to that in the reference product, or the excipient is present in the generic drug product in an amount typically used for that type of dosage form.

Examples of excipients known to have caused bioinequivalence that would not have been predicted by dissolution testing include surfactants, mannitol and sorbitol.

2. Biowaivers based on dose-proportionality of formulations

Under certain conditions, approval of different strengths of a generic product can be considered on the basis of dissolution profiles if the formulations have proportionally similar compositions as follows:

(i) All active and inactive ingredients are exactly in the same proportions in the different strengths (e.g. a tablet of 50 mg strength has all the active and inactive ingredients exactly half that of a tablet of 100 mg strength, and twice that of a tablet of 25 mg strength).

(ii) For a high potency APIs, where the amount of the APIs in the dosage form is relatively low (up to 10 mg per dosage unit), the total weight of the dosage form remains nearly the same for all strengths (within ±10% of the total weight), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering essentially only the amount of the APIs.

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is
that the generic product at one strength has been shown in \textit{in vivo} studies to be bioequivalent to the corresponding strength of the reference product. The second requirement is that the further strengths of the generic product are proportionally similar in formulation to that of the strength studied. When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to that of the strength studied on a percentage released against time basis, the biowaiver procedure can be considered for the further strengths.

A model independent mathematical approach (e.g. $f_2$ test) can be used for comparing the dissolution profile of two products. The dissolution profile of the two products (generic and reference) should be measured under the same test conditions.

The dissolution sampling times for both generic and reference product profiles should be the same:

- For example for immediate-release products 10, 15, 20, 30, 45 and 60 minutes;
- For example for 12 hour extended-release products 1, 2, 4, 6 and 8 hours; and
- For example for 24 hour extended-release products 1, 2, 4, 6, 8 and 16 hours.

Only one time-point should be considered after 85% dissolution from the reference product. An $f_2$ value of 50 or greater (50 –100) reflects equivalence (less than 10% difference) of the two curves, and thus equivalence of \textit{in vitro} performance of the two products. To allow the use of the mean data, the coefficient of variation should not be more than 20% at the earliest time-point (e.g. 10 minutes in the case of the example given for immediate-release products), and should not be more than 10% at other time points.

\textbf{a) Immediate-release tablets}

Different strengths of a generic formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:

(i) All strengths are proportionally similar in formulation (as mentioned before);

(ii) An appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength, unless a lower strength is chosen for reasons of safety); and

(iii) The dissolution profiles for the different strengths are similar.

If both strengths release 85% or more of the label amount of the APIs in 15 minutes, using all three dissolution media as previously recommended , the profile comparison with an $f_2$ test is unnecessary.
b) Delayed-release tablets and capsules
For delayed-release tablets, when the generic product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients and has the same delayed-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profile, $f_2>50$, in the recommended test condition for delayed release product, i.e. dissolution test in acid medium (pH 1.2) for 2 hours followed by dissolution in pH 6.8.
For delayed-release capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the APIs, similarity in the dissolution profile of the new (lower) strength to that of the approved strength ($f_2 >50$) under the test conditions recommended for delayed-release products is sufficient for a biowaiver.

c) Extended-release beaded capsules
For extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the APIs, dissolution profile comparison ($f_2 >50$) under one recommended test condition is sufficient for a biowaiver based on dose-proportionality of formulation.

d) Extended-release tablets
For extended-release tablets, when the generic product is in the same dosage form, but in a different strength, is proportionally similar in its active and inactive ingredients and has the same drug-release mechanism, a lower strength can be granted a biowaiver if it exhibits similar dissolution profiles, $f_2>50$, in three different pH buffers (between pH 1.2 and 7.5) by the recommended test method.

3. Biowaivers for scale-up and post-approval changes
Under certain conditions, following minor formulation or manufacturing changes after drug approval, *in vitro* dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics.
References


APPENDIX 1

Food-Effect Bioequivalence Studies

1. Study Design
A randomized, balanced, single-dose, two-treatment, two-period, two-sequence crossover design is recommended for food-effect bioequivalence studies. The test product and the reference listed drug product should be administered under fed conditions. An adequate washout period should separate the two treatments.

2. Subject Selection
Food-effect bioequivalence studies are usually carried out in healthy human volunteers. An adequate number of subjects should complete the study so as to achieve sufficient power for appropriate statistical assessment, but should not be less than 24.

3. Strength
Generally, the highest strength of a product should be tested in food-effect bioequivalence studies. In some cases, clinical safety concerns could warrants use of lower strengths of the dosage form. The lot and strength tested in the pivotal bioequivalence fasted study should be tested in the food-effect bioequivalence study.

When multiple strengths of MR drug products are intended for marketing and the food-effect study is performed on one of these strengths, in-vitro dissolution testing should be conducted for all other strengths in three different pH media. Similarity of dissolution should be established. Lack of similarity of dissolution could indicate that additional food-effect studies should be performed using other strengths.

4. Food Effect Meal
The primary food-effect bioequivalence study should be performed under conditions expected to provide maximal perturbation due to presence of food in the gastrointestinal tract. A high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast is therefore recommended as a test meal for food-effect bioequivalence study. Details of the meal should be recorded prior to the study and provided in the study protocol.

5. Administration
Following an overnight fast of at least 10 hours, subject should be served the food effect meal and ingest this meal within 20 minutes. The drug product should be administered with 150-250 ml of
water within 30 minutes after completion of the meal. No food should be allowed for at least 4 hours post-dose. Water can be allowed ad libitum after 2 hours. Subjects should be served scheduled standardized meals throughout the remaining study period.

6. Sample Collection
For both treatment periods, timed biological fluid samples should be collected from the subjects to permit characterization of the complete plasma concentration-time profile for the drug and/or metabolite(s). Caution should be used when studying MR dosage forms (e.g., enteric-coated products) where co-administration with food can delay in vivo drug release. In such instances, sampling times should be adjusted to obtain the complete plasma concentration-time profile.

7. Data and Statistical Analysis
The following measurements should be obtained from the resulting concentration-time profiles:

- Area under the concentration-time curve (AUC$_{0-t}$, AUC$_{0-\infty}$).
- Peak concentration (C$_{\text{max}}$).
- Time to peak concentration (t$_{\text{max}}$).
- Lag-time (t$_{\text{lag}}$) for delayed release products.

Individual subject parameters, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation, 90% confidence intervals {CI}) should be reported. The reference product administered under fed conditions should serves as the reference.

An equivalent food effect will be concluded when the 90% CI for the ratio of the means (population geometric means based on log-transformed data) of the test and the reference product fall within 80 –125% for AUC and C$_{\text{max}}$. In certain cases a wider interval of 75% to 133% for C$_{\text{max}}$ may be acceptable. If these CI criteria are not satisfied, the test formulation might not be considered equivalent to and interchangeable with the reference formulation. Clinical relevance of any change in t$_{\text{max}}$, and t$_{\text{lag}}$ should be considered.
Appendix II

Formatting of Bioequivalence Summary Tables

Table 1 Submission Summary

<table>
<thead>
<tr>
<th>Drug Product Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength(s)</td>
<td></td>
</tr>
<tr>
<td>Applicant Name</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Point of Contact</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Telephone Number</td>
<td></td>
</tr>
<tr>
<td>Fax Number</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Summary of Bioavailability Studies

<table>
<thead>
<tr>
<th>Study Ref. No.</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Treatments (Dose, Dosage Form, Route) Product ID</th>
<th>Subjects (No. (M/F) Type Age:mean (Range))</th>
<th>Mean Parameters (+/-SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (units/mL)</td>
</tr>
<tr>
<td>Study #</td>
<td>Fasting study title</td>
<td>Randomized single-dose crossover</td>
<td>Test product strength Tab./Cap./Susp. p.o. (Batch #)</td>
<td>#completing (#M#F) Healthy subjects or patients mean age (range)</td>
<td>M (%CV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reference product strength Tab./Cap./Susp. p.o. (Batch #)</td>
<td></td>
<td>M (%CV)</td>
</tr>
<tr>
<td>Study #</td>
<td>Fed study title</td>
<td>Randomized single-dose crossover</td>
<td>Test product strength Tab./Cap./Susp. p.o. (Batch #)</td>
<td>#completing (#M#F) Healthy subjects or patients mean age (range)</td>
<td>M (%CV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reference product strength Tab./Cap./Susp. p.o. (Batch #)</td>
<td></td>
<td>M (%CV)</td>
</tr>
</tbody>
</table>
Table 3 Statistical Summary of the Comparative Bioavailability Data

<table>
<thead>
<tr>
<th>Drug Dose(# x mg)</th>
<th>(Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted Bioequivalence Study (Study No.)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Test</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fed Bioequivalence Study (Study No.)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Test</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4 Bioanalytical Method Validation

<table>
<thead>
<tr>
<th>Information Requested</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioanalytical method validation report location</td>
<td>Provide the volume(s) and page(s)</td>
</tr>
<tr>
<td>Analyte</td>
<td>Provide the name(s) of the analyte(s)</td>
</tr>
<tr>
<td>Internal standard (IS)</td>
<td>Identify the internal standard used</td>
</tr>
<tr>
<td>Method description</td>
<td>Brief description of extraction method; analytical method</td>
</tr>
<tr>
<td>Limit of quantitation</td>
<td>LOQ, units</td>
</tr>
<tr>
<td>Average recovery of drug (%)</td>
<td>%</td>
</tr>
<tr>
<td>Average recovery of IS (%)</td>
<td>%</td>
</tr>
<tr>
<td>Standard curve concentration (units/mL)</td>
<td>Standard curve range and appropriate concentration units</td>
</tr>
<tr>
<td>QC concentrations (units/mL)</td>
<td>List all the concentrations used</td>
</tr>
<tr>
<td>QC Intraday precision range (%)</td>
<td>Range or per QC</td>
</tr>
<tr>
<td>QC Intraday accuracy range (%)</td>
<td>Range or per QC</td>
</tr>
<tr>
<td>QC Interday precision range (%)</td>
<td>Range or per QC</td>
</tr>
<tr>
<td>QC Interday accuracy range (%)</td>
<td>Range or per QC</td>
</tr>
<tr>
<td>Bench-top stability (hrs)</td>
<td>hours at room temperature</td>
</tr>
<tr>
<td>Stock stability (days)</td>
<td>days at 4°C</td>
</tr>
<tr>
<td>Processed stability (hrs)</td>
<td>hours at room temperature; hours at 4°C</td>
</tr>
<tr>
<td>Freeze-thaw stability (days)</td>
<td># cycles</td>
</tr>
<tr>
<td>Long-term storage stability (days)</td>
<td>17 days at -20°C (or other)</td>
</tr>
<tr>
<td>Dilution integrity</td>
<td>Concentration diluted X-fold</td>
</tr>
<tr>
<td>Selectivity</td>
<td>No interfering peaks noted in blank plasma samples</td>
</tr>
</tbody>
</table>

Please include table for each analyte.  
Please submit all Method Validation SOPs.
Table 5 Summary of In Vitro Dissolution Studies

<table>
<thead>
<tr>
<th>Dissolution Conditions</th>
<th>Apparatus:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Speed of Rotation:</td>
</tr>
<tr>
<td></td>
<td>Medium:</td>
</tr>
<tr>
<td></td>
<td>Volume:</td>
</tr>
<tr>
<td></td>
<td>Temperature:</td>
</tr>
</tbody>
</table>

Firm's Proposed Specifications

Dissolution Testing Site
(Name, Address)

<table>
<thead>
<tr>
<th>Study Ref No.</th>
<th>Testing Date</th>
<th>Product ID /Batch No. (Test-Manufacture Date) (Reference-Expiration Date)</th>
<th>Dosage Strength &amp; Form</th>
<th>No. of Dosage units</th>
<th>Collection Times (minutes or hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Report#:</td>
<td>Test Product</td>
<td>mg Tablet Capsule</td>
<td>12</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td></td>
</tr>
<tr>
<td>Study Report#:</td>
<td>Reference Product</td>
<td>mg Tablet Capsule</td>
<td>12</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%CV</td>
<td></td>
</tr>
</tbody>
</table>

Provide dissolution data for all strengths (test and reference).
Table 6 Formulation Data

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg) / Tablet</th>
<th>Amount (%) / Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength 1</td>
<td>Strength 2</td>
</tr>
<tr>
<td>Cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coating</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please include the formulation of all strengths.
Table 7 Demographic Profile of Subjects Completing the Bioequivalence Study

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product N=</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean±SD Range</td>
</tr>
<tr>
<td>Age Groups</td>
<td>18-35 35-55</td>
</tr>
<tr>
<td>Sex</td>
<td>Male Female</td>
</tr>
<tr>
<td>BMI*</td>
<td>Mean±SD Range</td>
</tr>
<tr>
<td>Other Factors</td>
<td></td>
</tr>
</tbody>
</table>

*BMI: Body mass index

Please provide a separate table for each Bioequivalence Study
Table 8 Incidence of Adverse Events in Individual

<table>
<thead>
<tr>
<th>Studies Body System / Adverse Event</th>
<th>Reported Incidence by Treatment Groups*</th>
<th>Fasted/Fed Bioequivalence Study** Study No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other organ sys.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Expressed as number and percentage  
**Provide separate table for each Bioequivalence Study
Table 9 Reanalysis of Study Samples

<table>
<thead>
<tr>
<th>Reason why assay was repeated</th>
<th>Number of samples reanalyzed</th>
<th>Number of recalculated values used after reanalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual number</td>
<td>% of total assays</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Pharmacokinetic*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason A (e.g. below LOQ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Please provide a separate table for each analyte measured for each in-vivo study.
<table>
<thead>
<tr>
<th>Table 10 Study Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Number</td>
</tr>
<tr>
<td>Study Title</td>
</tr>
<tr>
<td>Clinical Site</td>
</tr>
<tr>
<td>(Name, Address, Phone)</td>
</tr>
<tr>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Dosing Dates</td>
</tr>
<tr>
<td>Analytical site</td>
</tr>
<tr>
<td>(Name, Address, Phone)</td>
</tr>
<tr>
<td>Analysis Dates</td>
</tr>
<tr>
<td>Analytical Director</td>
</tr>
<tr>
<td>Storage Period of Biostudy</td>
</tr>
<tr>
<td>Samples (no. of days from</td>
</tr>
<tr>
<td>the first day of sample</td>
</tr>
<tr>
<td>collection to the last</td>
</tr>
<tr>
<td>day of sample analysis)</td>
</tr>
</tbody>
</table>

Please provide separate table for each Bioequivalence Study.
## Table 11: Product Information

<table>
<thead>
<tr>
<th>Product</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ingredient(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose Administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of Administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch/Lot No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch Size</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Manufacture Date</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Expiration Date</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Storage conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(to be attached)</strong></td>
<td></td>
<td><strong>(If available)</strong></td>
</tr>
<tr>
<td>Potency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content Uniformity (mean,%CV)</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 12 Dropout Information

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Subject No.</th>
<th>Reason for dropout/replacement*</th>
<th>Period</th>
<th>Replaced?</th>
<th>Replaced with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please provide separate table for each Bioequivalence Study.

* Please provide time, treatment (test or reference), and cause of dropout, if reason of dropout is other than "personal reasons".
Table 13 Dropout Information

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Type</th>
<th>Subject#s (Test)</th>
<th>Subject#s (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please provide a separate table for each Bioequivalence Study
Table 14 Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Curve Samples</th>
<th>Quality Control Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (ng, mcg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter day Precision (%CV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter day Accuracy (%Actual)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linearity</td>
<td>(Range of $R^2$ values)</td>
<td></td>
</tr>
<tr>
<td>Linearity Range (ng, mcg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity/LOQ (ng, mcg/ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If applicable, please provide separate tables for the parent drug and metabolite(s)
Table 15 SOP's Dealing with Bioanalytical Repeats of study samples*

<table>
<thead>
<tr>
<th>SOP No.</th>
<th>Effective Date of SOP</th>
<th>SOP Title</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Please include the SOP for Bioanalytical Repeats in your submission.
Table 16 Composition of Meal Used in Fed Bioequivalence Study

<table>
<thead>
<tr>
<th>Composition</th>
<th>Percent of total Kcal</th>
<th>Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>