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Drug Safety Center

Guideline on Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Drug Safety Center

2026

First Edition

Document Title	Guideline on Bioequivalence for Immediate-Release Solid Oral Dosage Forms
Document Type	Guideline
Directorate/Institution	Drug Safety Center (DSC)
Targeted Group	Applicants for marketing authorizations, Pharmaceutical Companies/ manufacturers, Contract research organization (CRO), Health care policy makers, DSC (BE Assessors), DSC CROs Inspectors.
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Release Date	July 2026
Review Frequency	Every 3 years

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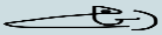
Signature		**Signature**	
Date	**23/07/2026**	**Date**	**29/07/2026**

Acknowledgments

The preparation of this guideline was undertaken by Ph. Azza Al-Ghammari, Ph. Hana Al-Rashdi, Ph. Jihad Al-Qassabi. The Drug Safety Center extends its sincere gratitude to all staff members of the section for their dedicated efforts. Special acknowledgment is given to the members of the Global Benchmark Tool (GBT)Task Force for their invaluable contributions, in particular:

- Ph. Hussain Al Ramimmy, Global Benchmark Tool (GBT) task force.
- Dr. Mohannad Elkhider, Global Benchmark Tool (GBT) task force.
- Ph. Suhaila Al Adawi, Global Benchmark Tool (GBT) task force.
- Ph. Safiya Al Aghbari, Global Benchmark Tool (GBT) task force.

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Acronyms

AUC	Area under the concentration vs. time curve
AUC (0-∞)	Area under the concentration vs. time curve extrapolated to infinity
AUC(0-72h)	Area under the concentration vs. time curve from time 0 to 72 hours
$AUC_{(0-t)}$	Area under the concentration vs. time curve from time zero to the time of last quantifiable concentration
Cmax	Maximum concentration observed after dosing
CmaxSS	Maximum concentration observed during dosing interval at steady-state
CminSS	Minimum concentration observed during dosing interval at steady-state
Fluctuation	Calculated as [(CmaxSS-CminSS) / CavSS]
kel	The apparent terminal elimination rate constant
pAUC	Area under the concentration vs. time curve between two specific time points
Swing	Calculated as [(CmaxSS – CminSS) / CminSS]
t1/2	The apparent terminal elimination half-life
Tau	Dosing Interval
tmax	Time to maximum observed concentration

Definitions

Applicant	The entity submitting the application for marketing authorization to the relevant regulatory authority.
Batch number (or Lot Number)	A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.
Chewable tablets	An oral dosage form designed to facilitate chewing and swallowing by the patient rather than swallowing a whole tablet. They must be chewed or crushed before swallowing.
Comparator product	An investigational or marketed product, i.e., active control, or placebo, used as a reference in a clinical trial. In the context of this guideline, a comparator product is the drug product accepted by regulatory agencies that an applicant can use to compare against the test product in conducting a BE study.
Enantiomers	Compounds with the same molecular formula that differ in the spatial arrangement of atoms within the molecule and are no superimposable mirror images.
Endogenous compounds	Compounds already present in the body either because the body produces them or because they are present in a normal diet.
Immediate-release	Allows the drug to dissolve in the GI contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.
Orally disintegrating tablet	A solid dosage form which is designed to disintegrate and dissolve rapidly on contact with saliva when placed on the tongue or in the oral cavity, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with water.
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

CHAPTER ONE

Introduction

Marketing Authorization Applications should demonstrate product's safety and efficacy through bioequivalence (BE) studies. This guideline is intended to provide recommendations on conducting (BE) studies during development for orally administered immediate-release (IR) solid dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. Deviations from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided. Applicants are encouraged to consult the regulatory authority when an alternate approach is proposed or taken.

Purpose

This Guideline provides recommendations for designing, conducting, and analyzing bioequivalence (BE) studies of orally administered immediate-release solid dosage forms. It ensures generic and innovator products have similar absorption rates and extents, confirming therapeutic equivalence, efficacy, and safety. The focus is on clinical pharmacokinetic endpoints and in vitro dissolution studies, supporting reliable and high-quality data in line with Good Clinical Practice and bioanalytical validation standards.

Scope

This guideline describes the scientific and technical aspects of study design and data analysis to support BE assessment based on PK endpoints for orally administered IR solid dosage forms.

Structure

This is the first version of this guideline and is organized into four chapters. CHAPTER ONE covers the Introduction, Purpose, Scope, and Structure. CHAPTER TWO outlines the detailed procedures and methods. CHAPTER THREE defines responsibilities in relation to this guideline. CHAPTER FOUR includes the document history and version control and references.

CHAPTER TWO

Procedure

2. Study Design for Pharmacokinetic Endpoint Bioequivalence Studies

2.1 Study Population

The selection of subjects for (BE) studies should aim to enable the detection of any differences in the in vivo release characteristics between pharmaceutical products. To minimize variability unrelated to product differences, these studies are generally conducted in healthy volunteers—unless safety concerns make this unethical. In most cases, studies in healthy subjects are sufficient to identify formulation performance differences and to extrapolate the results to the intended patient population. However, if the active substance is known to cause adverse effects or poses unacceptable risks to healthy individuals, the study may instead be conducted in the target patient population under appropriate medical supervision and safety precautions.

The study protocol must clearly define the inclusion and exclusion criteria for participants. Subjects should be at least 18 years old and preferably have a Body Mass Index (BMI) between 18.5 and 30.0 kg/m^2. When the drug product is intended for use in both sexes, inclusion of both male and female participants should be considered.

All participants should undergo screening to confirm suitability, including clinical laboratory tests, medical history evaluation, and physical examination. Depending on the therapeutic class and safety profile of the drug, additional medical assessments and safety measures may be required before, during, and after the study. Female subjects of reproductive potential must be carefully assessed for risk, and pregnant or lactating women should be excluded. Male subjects should use contraception (e.g., barrier methods or abstinence) if the drug poses embryo-fetal toxicity or transferability risks to female partners.

Subjects should ideally be non-smokers and free from any history of alcohol or substance abuse. Phenotyping and/or genotyping may be considered when relevant for safety or pharmacokinetic (PK) reasons.

2.2 Study Design

A randomized, single-dose, crossover study design is generally recommended for comparing test and reference formulations, as single-dose studies provide the most sensitive conditions for detecting differences in the rate and extent of drug absorption. Each treatment period should be separated by an adequate washout interval, typically corresponding to at least five elimination half-lives.

In most cases, the highest marketed strength of the product should be used in the BE) study. However, if administering the highest strength to healthy volunteers poses safety or tolerability concerns, a single-dose study using a lower strength in healthy subjects may be acceptable. Alternatively, a single-dose study in patients using the highest proposed strength may be considered.

A multiple-dose study may be appropriate in patients if a single-dose study is not feasible—either due to safety or tolerability issues in healthy subjects or ethical constraints in patients. For such studies, the protocol should include an adequate number of dosing administrations to achieve steady-state conditions. This should be demonstrated through an appropriate sampling schedule, where concentrations at the end of the dosing interval are collected sequentially until Ctau becomes stable. Steady-state attainment is typically confirmed by comparing at least three consecutive pre-dose concentrations for each formulation.

A complete washout of the last dose from the first treatment period is not always required before initiating the next treatment. However, the number of doses in the subsequent treatment period should be sufficient to establish a new steady-state and ensure elimination of the previous drug, generally corresponding to at least five elimination half-lives.

For drugs with long elimination half-lives, a randomized parallel design may be employed when a crossover design is impractical due to the extended washout period required.

Alternative study designs may also be acceptable if they are scientifically justified.

2.3 Sample Size for Bioequivalence Studies

The number of subjects included in a (BE) study should be determined based on an appropriate sample size calculation designed to achieve the desired statistical power. The sample size should be sufficient enough to accommodate potential dropouts or withdrawals during the study. The inclusion of spare or replacement subjects is not acceptable.

If the number of evaluable subjects falls below the required sample size, additional cohort(s) may be enrolled; however, this must be pre-specified in the study protocol and implemented before any bioanalytical results are available.

For pivotal BE studies, the number of subjects with evaluable data for the primary statistical analysis should be at least 12 in a crossover design, or at least 12 per treatment group in a parallel design.

2.4 Test and Comparator Product

A comparator product is the reference drug product recognized by regulatory authorities that serves as the basis for comparison with the test product in a (BE) study.

The selection of the comparator product batch should be guided by its assayed content. When choosing the batch for the BE study, it is advisable to evaluate more than one batch of the comparator product to ensure representativeness.

The test product used in the BE study should be representative of the formulation intended for marketing, and this must be appropriately justified and discussed by the applicant.

For pivotal BE studies, oral test products should meet the following criteria:

a) Batch size and manufacturing feasibility: The batches used should provide a high level of confidence that both the product and the manufacturing process are scalable to commercial production. For example, for tablets and capsules, the test product should normally be manufactured from a batch of at least one-tenth of the production scale or 100,000 units—whichever is greater—unless otherwise justified. If the total production batch is smaller than 100,000 units, a full production batch should be used.

b) Assayed content consistency: Unless otherwise justified, the assayed content of the test product batch should not differ by more than 5% from that of the comparator product batch.

2.5 Fasting and Fed Study Conditions

(BE) studies should be performed under standardized conditions that minimize variability to allow better detection of (PK) differences between drug products. For (IR) solid dosage forms, single-dose BE studies conducted under fasting conditions generally offer greater sensitivity in detecting differences between the PK profiles of two drug products compared with studies conducted under fed conditions. Therefore, for most such products, BE can be demonstrated in a single study conducted under fasting conditions.

However, food can have a formulation-dependent effect on the absorption of certain drug products with special characteristics, which increases the risk of bio inequivalence due to food effects (see “High-risk products” section below). In these cases, bioequivalence under fed conditions must also be demonstrated, as extrapolation from fasting to fed conditions may not be appropriate.

Additionally, some drug products—though not complex in formulation or manufacturing—may still possess characteristics that influence the food effect. For such products, both fasting and fed studies are required unless scientifically justified. Acceptable justification may be supported by factors such as formulation differences (qualitative or quantitative excipient variations), Biopharmaceutics Classification System (BCS) classification, in vitro studies (e.g., disintegration or dissolution testing in biorelevant media), pilot studies, or validated modelling approaches such as physiologically based pharmacokinetic (PBPK) modelling and simulation, or semi-mechanistic absorption models that are fit for purpose.

When BE studies are required, the same principles for fasting and fed study conditions also apply to studies conducted to bridge formulation or manufacturing process changes during pre- or post-marketing phases. Scientific justification, including available relative bioavailability (BA) and food effect data, may be provided to support any deviation from these principles.

2.5.1 High Risk Products

High-risk products are those in which the characteristics of the drug substance, combined with the complexity of the formulation design or manufacturing process, increase the likelihood that in vivo performance will be affected differently under fasting and fed gastrointestinal (GI) conditions.

For such products, differences in performance due to formulation or manufacturing variability may not be detected through a single (BE) study. In other words, the results from a fasting BE study cannot be reliably extrapolated to predict outcomes under fed conditions, or vice versa. Therefore, both fasting and fed BE studies should be conducted.

For example, certain drug products containing low-solubility drug substances employ complex formulation or manufacturing techniques—such as solid dispersions, micro emulsions, co-processed drug substances, lipid-based formulations, nanotechnologies, or other advanced technologies—to enhance solubility, promote drug release, or mitigate food effects.

Accordingly, for these high-risk products, BE studies must be performed under both fasting and fed conditions, regardless of the product's labelling regarding food intake, provided it is safe to do so.

2.5.2 Considerations for study design

The design of (BE) study, with respect to fasting and/or fed conditions, should be guided by both the dosing instructions of the comparator product and the characteristics of the drug substance and formulation of the test product. A clear justification must be provided for the selection of the type of BE study (fasting, fed, or both) and the meal composition, including fat and calorie content, based on the properties of the comparator and test products, and whether the product is considered high- or non-high-risk.

Safety considerations should also inform the choice of study conditions. If administering a single dose under either fasting or fed conditions raises safety concerns, the study should be conducted under the condition associated with lower risk.

If safety allows, the following recommendations apply to non-high-risk products:

- For products labelled to be taken only under fasting conditions, or without regard to food, a single BE study under fasting conditions is recommended.
- For products labelled to be taken only with food for pharmacokinetic (PK) reasons, such as enhancing absorption or reducing variability, a single BE study under fed conditions is recommended.
- For products labelled to be taken only with food for tolerability reasons, such as stomach irritation or other non-PK concerns, a BE study under either fasting or fed conditions is acceptable.

For high-risk products, BE studies should be conducted under both fasting and fed conditions, regardless of the product's food labelling, provided safety permits.

When BE studies are needed under both fasting and fed conditions, it is acceptable to conduct either two separate two-way crossover studies or a single four-way crossover study.

2.5.3 Standardization with regard to meals and water

For BE studies conducted under fasting conditions, subjects should fast for at least 8 hours prior to drug administration. Water may be consumed as desired, except for 1 hour before and 1 hour after dosing. The drug should be administered with water of consistent temperature and volume, typically between 150 and 250 milliliters. In single-dose studies and on PK sampling days in multiple-dose studies, no food should be allowed for at least 4 hours after dosing. Meals consumed during the in-house portion of the study should be standardized in terms of composition and timing.

For studies conducted under fed conditions, similar controls apply, except that a pre-dose meal must be provided. Subjects should begin the meal approximately 30 minutes before drug administration and finish it within 30 minutes.

In BE studies conducted under both fasting and fed conditions (e.g., for high-risk products), the fed study should use a meal likely to have the greatest effect on gastrointestinal physiology. The recommended meal is high-fat (around 50% of total calories) and high-calorie (approximately 900–1000 kcal), with about 150 kcal from protein, 250 kcal from carbohydrates, and 500–600 kcal from fat. In some cases, adjustments to caloric or fat content may be necessary, for example in patient populations unable to tolerate the standard meal.

For non-high-risk products requiring only a fed study, either a high-fat, high-calorie meal or a lower-fat, lower-calorie meal (approximately 500 kcal, with ~25% calories from fat) may be used. If the comparator product labeling specifies a meal type, that meal should be used.

The meal composition should be clearly described in the study protocol, including grams, kcal, and relative caloric content (%) of protein, carbohydrate, and fat.

Regardless of study type, subjects should avoid foods and beverages known to interfere with GI, hepatic, renal, or circulatory function (e.g., alcohol, caffeine, grapefruit juice) before and during the study. Additionally, posture and physical activity should be standardized, as these factors can influence gastrointestinal transit and regional blood flow, which may affect drug absorption.

2.6 Dose or Strength to be Studied

For drug products with multiple strengths, the strength used in a BE study depends on the drug's dose proportionality in (PK) and the solubility of the drug substance. Typically, the highest marketed strength can be tested as a single unit. A lower strength may be considered if the highest strength cannot be safely administered to healthy subjects, provided that dose-proportional PK has been demonstrated across the range of strengths based on C_max and AUC.

To ensure adequate bioanalytical sensitivity, multiple units of the highest strength may be given as long as the total single dose remains within the labeled range and is safe for subjects.

Determining dose proportionality:

- Refer to the approved comparator product labeling.
- If information is unavailable, use all relevant sources of data.
- Dose proportionality is generally assessed using single-dose studies, with C_max and AUC as key PK parameters.
- PK is typically considered dose proportional if the difference in dose-adjusted mean C_max and AUC is ≤25% across the proposed range of strengths.

For additional strength waivers, both AUC and C_max are evaluated. However, if data for C_max are insufficient (e.g., due to high variability) but dose proportionality for AUC is established, the PK can still be considered dose proportional.

If dose proportionality cannot be established, BE studies should include both the lowest and highest strengths.

Non-proportional PK:

- If AUC or C_max increases more than proportionally with dose, BE studies should generally be conducted at the highest strength.
- If AUC or C_max increases less than proportionally due to absorption saturation, the BE study should focus on the lowest strength.

If the less than proportional increase is due to limited solubility or the reason is unknown, BE studies should be conducted with both the lowest and highest strengths

For high-risk products, typically:

- A fasting and fed BE study at the highest strength
- A fasting BE study at the lowest strength

2.7 Moieties to be Measured

2.7.1 Parent vs. Metabolite

(BE) should generally be demonstrated using the parent drug, as its concentration-time profile is typically more sensitive for detecting differences between formulations. This approach also applies to prodrugs.

However, for some prodrugs, the parent drug is rapidly eliminated, resulting in plasma concentrations that are too low for reliable measurement. In such cases, BE may be established using a primary metabolite (i.e., the first-step metabolite of the parent drug) without measuring the parent compound.

In rare situations, evaluating the parent drug alone may be insufficient. The primary active metabolite should also be considered, particularly when metabolites formed via gut wall or gut lumen metabolism contribute to efficacy or safety. This ensures that potential formulation-related differences affecting metabolite formation are not overlooked when only the parent drug is measured.

2.7.2 Enantiomers vs. Racemates

- The use of an achiral bioanalytical assay to measure the racemic mixture is generally acceptable. However, a stereoselective assay that quantifies individual enantiomers should be employed in BE studies if all of the following conditions are met: The enantiomers exhibit different (PD) properties.
- The enantiomers exhibit different (PK) properties.
- Differences in absorption rates alter the exposure (AUC) ratio of the enantiomers.

If one enantiomer is inactive or contributes minimally to safety and efficacy, demonstrating BE for the active enantiomer alone is sufficient.

2.8 Consideration for Sampling Schedule

The sampling schedule in a BE study should adequately capture the full concentration-time profile. This includes:

A pre-dose sample.

Samples during the absorption phase.

Frequent samples around the expected t_{max} (time of maximum observed concentration).

Sufficient samples during the elimination phase to reliably estimate the extent of exposure. Typically, AUC(0-t) should cover at least 80% of AUC (0-∞).

The sampling duration should generally be at least three times the terminal elimination half-life of the drug, unless a suitable truncated AUC (e.g., AUC(0-72h)) is justified. A sufficient number of samples should be collected per subject in each study period, covering all phases of disposition to allow calculation of relevant PK parameters.

Exact sample times should be recorded to calculate elapsed time relative to drug administration. Sampling should be planned to accurately determine C_{max}, AUC(0-t), and the apparent terminal elimination rate constant (k_{el}).

Since estimating k_{el} from a small number of data points may introduce considerable inaccuracies, it is recommended to use three or more points in the terminal log-linear phase of the concentration-time curve.

In multiple-dose studies, the pre-dose sample should be taken immediately before dosing (within 5 minutes), and the last sample should be taken within 10 minutes of the nominal end of the dosing interval to ensure accurate estimation of AUC(0-tauSS).

2.8.1 First Point C max

The sampling schedule should include frequent measurements around the expected t_{max} to ensure an accurate estimation of C_{max}. Careful planning is needed to avoid having C_{max} coincide with the first post-dose sample, taking into account the known pharmacokinetics of the drug and selecting appropriate early sampling time points.

For drugs with rapid absorption, early blood samples are typically collected between 5- and 15-minutes' post-dose, followed by additional 2–5 samples within the first hour to reliably capture peak concentrations. Sampling earlier than 5 minutes is generally unnecessary.

If C_{max} occurs at the first post-dose sample for a subject, the true peak may have been missed, potentially affecting study robustness. In such cases, it is recommended to discuss the impact on study results. Analyses could include sensitivity checks, such as removing data from affected subjects to evaluate potential effects on overall conclusions.

2.8.2 Long half-life drugs and truncated AUC Consideration

For orally administered (IR) drug products with long elimination half-lives (≥24 hours), truncating the AUC can help reduce the practical challenges of extended sampling and follow-up. In these cases, AUC(0–72h) may be used instead of AUC(0-t) to assess the extent of absorption. A 72-hour sampling period is generally sufficient to allow for complete gastrointestinal transit of the drug product and absorption of the active substance.

2.8.3 Early Exposure

For orally administered (IR) drug products, (BE) is usually assessed by measuring the rate and extent of absorption, specifically Cmax and AUC(0–t). However, in certain situations, these parameters alone may not be sufficient to fully evaluate BE, such as when the early onset of action is clinically important. In such cases, additional (PK) metrics—like the partial AUC (pAUC) or tmax—may be used.

When using pAUC, it is typically calculated from the time of drug administration up to a predetermined time point linked to a clinically relevant pharmacodynamics effect. Sampling should be appropriately timed to ensure accurate estimation of the pAUC.

2.9. Data Analysis for Non-Replicate Study Design

2.9.1 Consideration for the Bioequivalence Analysis Population

It is essential that the study protocol clearly specifies all criteria for including or excluding subjects from the bioequivalence (BE) analysis population. Any exclusions, such as subjects who are withdrawn, have protocol violations, or experience gastrointestinal (GI) disturbances that could affect drug absorption, should be documented before the bioanalytical analysis is conducted.

2.9.2 Removal of Data to Low Exposure

(BE) studies typically involve fewer subjects than other clinical trials. Therefore, an extreme value in the dataset can significantly influence the study outcome. While statistical tests may identify such extreme values in (PK) parameters, these data should not be excluded from the BE analysis solely on that basis. Removal of data should only occur due to protocol violations that are contemporaneously documented, and a prospective plan for data exclusion should be specified in the study protocol.

An exception may be made for subjects with unmeasurable or extremely low concentrations following administration of either the test or comparator product. A concentration is considered very low if the subject's AUC for that period is less than 5% of the geometric mean AUC of the drug product, calculated excluding the subject's own data. Such low concentrations are typically due to non-compliance, which should be minimized by measures such as mouth checks after dosing to ensure the drug was swallowed. Exclusion of data for this reason is acceptable only in exceptional cases, generally limited to one subject per study, and may raise questions about dose administration reliability.

Data from redosing studies, where a subset of subjects is dosed again, cannot justify the removal of extreme values from the statistical analysis.

All subject data should be submitted, and any potential extreme values should be flagged with appropriate documentation as part of the regulatory application.

2.10 Presentation of Data

2.10.1 Concentration Time Data

For both the test and comparator products, drug concentrations in an appropriate biological fluid, such as plasma, serum, or blood, should be tabulated for each subject at every sampling time point, along with descriptive statistics. Data should be presented on the original scale, meaning the measured drug concentrations without adjustment. Any protocol deviations, such as missed samples or samples collected outside the scheduled time window, should be clearly indicated.

Two types of concentration-time plots—linear and log-linear—should be generated for each individual subject for both the test and comparator products. Additionally, linear and log-linear plots should be produced for the mean concentrations across all subjects for both products. For individual plots, drug concentrations should be plotted against the actual sampling times, whereas for mean plots, concentrations should be plotted against the nominal sampling times.

2.10.2 Pharmacokinetic Analysis

For single-dose studies, the following pharmacokinetic (PK) parameters should be tabulated for each subject–formulation combination:

1. Primary parameters for BE analysis:
    - AUC(0-t), Cmax, and, if applicable, early exposure parameters.
2. Additional parameters to assess the study's acceptability:
    - AUC (0-∞), AUC(0-t)/AUC (0-∞), tmax, kel, and t1/2.

For single-dose studies, AUC(0-t) should cover at least 80% of AUC (0-∞). If more than 20% of observations fall below this threshold, the validity of the study may need to be addressed in the submission. For long half-life drugs where AUC is truncated at 72 hours, the primary

parameter is AUC(0-72h); additional parameters such as AUC (0-∞), AUC(0-t)/AUC (0-∞), kel, and t1/2 are not required.

Summary statistics should include the number of observations, geometric mean, coefficient of variation, median, arithmetic mean, standard deviation, minimum, and maximum. PK parameters must be calculated using actual sampling times, and the non-compartmental methods used (e.g., linear trapezoidal method for AUC) as well as the number of data points used to estimate kel should be reported.

For multiple-dose studies, the protocol should document proper dosage administration and sampling to demonstrate steady-state attainment. For steady-state studies, tabulated PK parameters should include:

1. Primary parameters for analysis:
    - CmaxSS and AUC(0-tauSS).
2. Additional parameters:
    - CtauSS, CminSS, CavSS, degree of fluctuation, swing, and tmax.

Any concentrations below the lower limit of quantification (LLOQ) should be treated as zero when calculating PK parameters, but values below LLOQ should be excluded from calculations of kel and t1/2.

2.10.3 Potency Differences in Lots

The results of the potency assay for both the test and comparator products should be submitted. The potency of the test and comparator batches should generally not differ by more than 5%.

In rare situations where a comparator batch within 5% of the test product potency cannot be obtained, a potency correction may be considered. This requires supporting justification, such as data from multiple lots of the comparator product, pending market availability, and an assessment of the totality of evidence.

If a potency correction is planned, this must be specified in the study protocol. Analyses should be presented for both uncorrected and potency-corrected data. When the potency correction is

justified, the applicable bioequivalence (BE) criteria should be evaluated using the potency-corrected data.

2.11 Statistical Analysis

2.11.1 General Considerations

Statistical analyses should include all subjects providing evaluable data for the drug products being compared. Any decision to exclude subjects from the BE analysis population, for example due to incomplete sampling or protocol violations, should be documented at the end of the clinical blood sampling period and prior to bioanalytical analysis. A study will generally not be considered valid if there are fewer than 12 subjects with evaluable data for primary statistical analysis in a crossover design or per treatment arm in a parallel design.

In studies with more than two treatment arms, such as a four-period study examining fasting and fed conditions or a three-period study with multiple comparators or test products, each comparison should be analyzed independently, excluding data from irrelevant treatment arms.

Bioequivalence is assessed using 90% confidence intervals (CI) for the geometric mean ratios (test/comparator) of the primary PK parameters. Logarithmic transformation of the PK data should be performed prior to analysis.

The statistical model must be pre-specified in the study protocol, and the analysis should account for all sources of variation reasonably expected to affect the response. Post hoc or data-driven adjustments are not acceptable for the primary analysis.

The final analysis report should provide sufficient detail to allow replication of the PK and statistical analyses. This includes data on actual blood sampling times, measured drug concentrations, PK parameter values for each subject in each period, and the randomization scheme.

2.11.2 Crossover Design Studies

Randomized, non-replicate crossover studies should be analyzed using a suitable parametric approach, such as a general linear model (GLM) or a mixed-effects model. All resulting tables

from these analyses, including the relevant statistical tests for each effect in the model, should be submitted. For example, summaries of the tests for sequence, subject within sequence, period, and formulation effects should be provided.

The primary statistical analysis must include all subjects providing evaluable data for both the test and comparator products.

2.11.3 Carry-over

Testing for carry-over effects is generally not considered relevant, and no analysis decisions, such as analyzing only the first period, should be based on such tests. In crossover studies, the potential for carry-over can be more appropriately evaluated by examining pre-dose plasma concentrations in period 2 and subsequent periods, for example, period 3 in a three-period study.

For single-dose studies, if a subject's pre-dose concentration exceeds 5% of the Cmax for that subject in that period, the primary statistical analysis should be conducted excluding the data from that period, which may lead to the exclusion of the subject from the analysis.

2.11.4 Parallel Design Studies

For randomized, parallel design studies, the statistical analysis should treat the samples as independent. Demographic characteristics and other relevant covariates that could influence pharmacokinetics (PK) should be balanced between groups whenever possible. It is recommended to use stratification during randomization based on a small number of known relevant factors. These factors should also be included in the primary statistical analysis.

2.11.5 Multi-Group Design Studies

When sample size or study logistics require, BE studies may be conducted in groups of subjects. The study design should aim to minimize the effect of grouping. Multiple interacting factors can make group assignments complex.

Bioequivalence should be assessed based on the overall treatment effect across the entire study population. The statistical model should account for the multi-group structure of the study, for example by including terms for group, sequence, sequence × group, subject within sequence × group, period within group, and formulation. The group × treatment interaction term should not be included in the primary model. Applicants should, however, assess the potential for heterogeneity of treatment effects across groups and discuss its possible impact. This can be done through supportive analyses, such as evaluating the group × treatment interaction or calculating descriptive statistics by group.

In multi-center BE studies, if some sites have very few subjects, these subjects may be pooled into a single group for statistical analysis. Rules for pooling should be predefined in the study protocol, and a sensitivity analysis is recommended.

2.12 Bioequivalence Criteria

For the majority of drug products, the PK parameters to demonstrate BE include C max and AUC(0-t) in single-dose studies and C maxSS and AUC(0-tauSS) in multiple-dose studies.

For drugs with a long elimination half-life, AUC(0-72h) may be used as AUC(0-t).

The 90% confidence interval for the geometric mean ratio of these PK parameters used to establish BE should lie within a range of 80.00 - 125.00%.

For drugs where it is clinically relevant to assess the early exposure or early onset of action, an additional PK parameter should be used to establish BE.

2.13 Multiple Comparator and Multiple Test Product Studies

2.13.1 Multiple Comparator Products

In certain cases, it may be necessary to demonstrate bioequivalence between a test product and multiple comparator products to satisfy the requirements of different regulatory jurisdictions. Including comparator products from different regions in a single trial is acceptable and can streamline the BE evaluation by conducting one higher-order crossover study encompassing multiple comparator products.

For studies with multiple comparator products, multiplicity correction (alpha adjustment) is not required, as each comparator product is considered independent and specific to its region. Decisions regarding bioequivalence are made independently for each test-comparator pair within a specific jurisdiction.

It is possible that the test product meets the BE criteria with one region-specific comparator but fails to meet them with another comparator. In such cases, BE is confirmed for the comparator product that meets the criteria and not for the one that does not. The study protocol should clearly define the primary objectives and specify which comparisons will be conducted.

All results from the multiple comparisons should be fully reported in the clinical study report.

2.13.2 Multiple Test Product

In some cases, it may be necessary to demonstrate bioequivalence between multiple test products and a single comparator product, for example, when different test formulations need to be evaluated during drug development. To simplify the BE assessment, it is permissible to conduct a single crossover BE study that includes multiple test products.

The requirement for multiplicity correction in pivotal trials depends on the objective of the study:

a) If the objective is to demonstrate BE for all test formulations relative to the comparator, no alpha adjustment is required.

b) If the objective is to demonstrate BE for any one of the test formulations, a multiplicity (alpha) adjustment may be necessary.

The study protocol should clearly pre-specify the trial objective and, if applicable, the method for multiplicity correction.

2.14 SPECIFIC TOPICS

2.14.1 Endogenous Compounds

For some drugs, the administered compound is identical to an endogenous substance, making it difficult to determine how much of the drug is released from the dosage form and absorbed for bioequivalence assessment. In these cases, it is usually necessary to measure baseline endogenous concentrations in biological matrices, such as blood, plasma, or urine, and subtract them from the total concentrations measured after drug administration.

If diet influences endogenous levels, dietary intake should be restricted or standardized before and during the study. The method for baseline correction should be pre-specified and justified in the study protocol. Multiple baseline measurements should be taken for each subject prior to dosing. Post-dose concentrations are then corrected by subtracting either time-averaged (mean or median) or time-matched baseline concentrations, depending on the pharmacokinetic characteristics of the drug.

Baseline concentrations should be determined separately for each study period, and corrections should be period-specific. Washout periods must be long enough to avoid carry-over effects. If baseline correction yields a negative concentration, the value should be set to zero.

Both baseline uncorrected and baseline corrected data should be analyzed pharmacokinetically and statistically, but BE determination is generally based on baseline corrected data.

When needed to ensure adequate separation of treatment-induced concentrations from baseline, a higher dose may be administered if well tolerated and pharmacokinetics remain dose-proportional. Alternatively, subjects with low or no endogenous production can be enrolled to minimize the need for baseline correction.

2.15 Other Immediate Release Dosage Forms

2.15.1 Orally Disintegration Tablets

In bioequivalence studies, orally disintegrating tablets (ODTs) should be administered in accordance with the comparator product's labeling, specifically regarding water intake.

- If the comparator product allows the ODT to be taken with or without water, both test and comparator products should be administered without water, as this scenario is

generally more discriminating. Bioequivalence of the products taken with water can then be inferred.

- For new intended labeling, such as ODTs intended as an extension of another orally administered IR drug, bioequivalence studies should reflect the intended use of the ODT and compare it with the comparator product administered according to its labeling.
- If the new labeling indicates that the ODT can be taken with or without water, a three-arm study is recommended to demonstrate bioequivalence of the ODT with water, without water, and the comparator product.

For studies evaluating ODTs without water, it is recommended that the mouth be moistened by swallowing a small volume of water (e.g., 20 mL) immediately before placing the ODT on the tongue. No fluid intake should be allowed for at least 1 hour after administration.

Other orally dispersible formulations, including Oro dispersible films, buccal tablets or films, and sublingual tablets, can generally be handled in the same manner as ODTs.

2.15.2 Chewable Tablets

In bioequivalence studies, chewable tablets should be administered according to the comparator product's labeling, specifically regarding water intake.

- If the comparator product allows the chewable tablet to be taken with or without water, both test and comparator products should be administered without water, as this is generally considered the more discriminating scenario. Bioequivalence of the products taken with water can then be inferred.
- For new intended labeling, such as chewable tablets intended as an extension of another orally administered IR drug, bioequivalence studies should reflect the intended use of the chewable tablet and compare it with the comparator product administered according to its labeling.
- If the new labeling indicates that the chewable tablets can be taken with or without water, a three-arm study is recommended to demonstrate bioequivalence of the chewable tablets with water, without water, and the comparator product.

2.15.3 Oral suspension

For tablets, granules, and powders that are intended to be dispersed in a liquid before administration as an oral suspension, bioequivalence (BE) studies should follow the comparator product's labelling instructions.

For new intended uses or instructions, such as using an oral suspension as an extension of another orally administered immediate-release (IR) drug, BE studies can be performed to assess whether the oral suspension is bioequivalent to the comparator product.

In such cases, the oral suspension should be administered according to its intended labelling, and the comparator product should be administered according to its approved labelling.

2.16 Fixed Dose Combination

The bioequivalence (BE) study design for fixed-dose combination (FDC) products should adhere to the principles outlined in this guideline.

BE should be evaluated using a pharmacokinetic (PK) sampling schedule appropriate for measuring the PK parameters of each individual drug in the combination.

Bioanalytical methods must be validated to accurately measure each drug in the presence of the other component(s) of the FDC product.

The PK parameters assessed and reported for each drug should be the same as those required if the drug were administered as a single-entity formulation.

BE must be demonstrated for all components of the FDC product. If BE is not demonstrated for even one component, the entire FDC product is considered not bioequivalent.

BE of the components can be established either in a single study covering all drugs or in separate studies for each component, if justified.

2.17 Ph-Dependency

The absorption of drugs with pH-dependent solubility can be influenced by gastric pH, and this effect may be modified by the use of pH-altering excipients or a specific salt form in the formulation. Additionally, the formulation of the marketed comparator product may have been optimized to avoid pH-related absorption issues.

In certain situations, an additional BE study with concomitant administration of a pH-modifying agent may be necessary if all of the following conditions are met:

1. The drug substance exhibits pH-dependent solubility in the pH range of 1.2–6.8.
2. The drug product is likely to be co-administered with acid-reducing agents (e.g., proton pump inhibitors) or used in populations with altered gastric pH, such as achlorhydric patients.
3. There are qualitative or quantitative differences in pH-modifying excipients, significant manufacturing differences that could affect absorption due to gastric pH, or differences in salt or polymorphic forms that alter pH-dependent solubility.

Study conditions:

- For non-high-risk products, the study with concomitant pH modification should follow the same fasting or fed conditions as the standard BE study.
- For high-risk products, a fasting BE study with pH-modifying agent is generally required in addition to standard fasting and fed BE studies.
- For products labeled to be taken only with food, the study with a pH-modifying agent should be conducted under fed conditions.

Applicants may provide a scientific justification if a BE study under altered gastric pH is deemed unnecessary. This justification should be based on the totality of evidence, including:

- pH-solubility profile of the drug,
- potential impact of excipients, formulation, and manufacturing design,
- differences between the test and comparator products, and
- comparative dissolution testing across multiple pH conditions.

2.18 Contract research organizations (CROs):

Requests to approve the CRO by the Drug safety center MOH Oman (**DSC) s**hould be submitted using the **Application Form for CRO Approval** (see Appendix 2).

CHAPTER THREE

Responsibilities:

Applicants for Marketing Authorizations	• Submit complete BE study data. • Select appropriate reference product. • Ensure study design meets guideline requirements. • Address regulatory queries.
Pharmaceutical Companies / Manufacturers	• Develop and manufacture the generic product under GMP • Ensure batch consistency for BE studies • Provide formulation and quality documentation • Oversee outsourced activities (CROs)
Contract Research Organizations (CROs)	• Conduct BE studies under GCP/GLP • Ensure ethical approvals • Use validated analytical methods • Maintain accurate data and complete study reports
Health Care Policy Makers	• Create policies supporting safe, effective, affordable generics • Strengthen regulatory capacity • Promote public trust in generic medicines
DSC BE Assessors	• Scientifically evaluate BE submissions • Review analytical, clinical, and statistical data • Ensure guideline compliance • Prepare assessment reports and recommendations
DSC CROs inspectors	• Verify compliance with guidelines while conducting inspections • Issue approvals or requests for additional information

CHAPTER FOUR

Document History and Version Control

Version	Description	Review Date
1	Initial Release	July 2026
2		
3		

References:

International Council for Harmonization (ICH) (2024), *ICH guideline M13 Bioequivalence for Immediate-Release Solid Oral Dosage Forms 2024.*

European Medicines Agency (EMA) (2010), *Guideline on Investigation of Bioequivalence 2010.*

Glossary of ICH terms and definitions *Compiled by CIOMS from the International Council for Harmonization (ICH)'s Version 8 5 June 2025.*

Annexes

Appendix 1: Bioequivalence Study Summary Template should be submitted within the Marketing Authorization Application

Bioequivalence Study Summary Template

DSC/PV/GUD/001/FRM001/Vers.1

Product (to be registered)		
Product Name (Trade name)		
Strength to be registered		
Active ingredients		
Therapeutic category		
Biopharmaceutical classification system BCS		
Attached BE summary form		
Test product and Reference product Information		
	Test drug (bio- batch)	**Reference drug**
Trade name		
Investigated strength		
Selection of reference product *(Should be registered in GCC, if not should be registered either in USFDA or EMA).*	NA	A) Registered in GCC B) Registered in USFDA C) Registered in EMA D) Other……

Dosage form *(Test and reference Should be the same, if different refer to the guidelines)*	
API source(s) used in bio batch *(Important for variation)*	NA
Particle size used in bio batch	NA
Polymorphic form of API in bio-batch	NA
The drug exhibits a linear Pharmacokinetics	
Narrow therapeutic index drug *(if yes, the acceptance interval for* *AUC should be tightened to 90.00-111.11%)*	
Highly variable drug *(intra-subject variability for a parameter is larger than 30%. Cmax can be widened to a maximum of 69.84 – 143.19%)*	
Type of formulation (Immediate, modified) *In case of Modified release product both of fast and fed studies should be conduct.*	
Bio-Batch Type	
Bio-Batch Size *The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. In case of a production batch*	NA

smaller than 100,000 units, a full production batch will be required	
Expected production size *(Shouldn't exceed 10 folds of the bio-batch size)*	NA
Batch number	
Manufacturing site	
Manufacturing date	
Expiry date	
Method of administration & effect of food:	
Assay content in the COA *(The differences between Bio-batch and reference should not exceed 5 %)*	
Dissolution content %	
Used media for dissolution in COA	
Study Center	Approved in GCC: ○ YES ○ No
Study Center	A) Clinical site: B) Diagnostic Laboratory tests: C) Bioanalytical site:
Study Code No.	

Protocol and its amendments (with dates and signatures) *The BE study should be conducted after the protocol approval dates)*	
The inclusion & exclusion criteria should be clearly stated in the protocol	
Study Dates; P I/PII	PI: -- / -- / ---- PII: -- / -- / ----
Bioanalytical dates	Start date from -- / -- / ---- to -- / -- / ----
Study Design	A Comparative, randomized, two periods, two sequence single dose cross over (standard design) B Parallel design (for long half-life) C Replicate design (for highly variable drugs CV more than 30%) D Truncated (72hours) design (long half-life) E. Other:
In Fasting study, Is the general protocol is followed: *Subjects should fast for at least 8 hours prior to administration of the products, unless otherwise justified. As fluid intake may influence gastric passage for oral administration forms, the test and reference products should be administered with standardized volume of fluid (at least 150 ml).* *It is recommended that water is allowed as desired except for one*	

hour before and one-hour after drug administration and no food is allowed for at least 4 hours' post-dose. Meals taken after dosing should be standardized in regard to composition and time of administration during an adequate period of time (e.g., 12 hours).	
Study condition: (Fast, Fed, Other) Fast study: for products where the SmPC recommends intake of the reference medicinal products on an empty stomach or irrespective of food intake.	
If fed study, is the meal satisfactory. *If no specific recommendation is given in the originator SmPC, the meal should be a high-fat (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).*	
Names and affiliation of the responsible investigator	

Principle investigator and bioanalytical investigator C. V	
Review board/ Ethical committee approvals *Date of the approval Should be before protocol date*	
Deviation from protocol, if any:	
Informed Consent Form *(Available, for all subjects, including signatures, witness)*	
Strength to be investigated if lower, please justify *(The studied strength should be the higher unless justified, e.g., low safety profile)*	
The acceptance range of 90% of CI for Cmax, AUC(0-t), AUC (0-∞) in the protocol If other, specify:	
Clinical Study Results *(including Results of drug/alcohol/smoking usage, medical history and medical examination, vital sign and diagnostic laboratory test of subjects).*	
Adverse event/reaction reports for test product and reference product.	
Reasons of withdrawal of subjects	

<table>
<tr><td>permitted reasons for exclusion must be pre-specified in the protocol</td><td colspan="4"></td></tr>
<tr><td>Case report form

(Available for all subjects, all screening data available, Date of screening (should be no longer than 2 –3 weeks prior to study)

Includes all laboratory tests specified in the protocol

Includes physical examination:

All laboratory test results are available</td><td colspan="4"></td></tr>
<tr><td>Drug accountability
Available:
Total consumed units:
Remaining units:
No of consumed units matching with the remaining:</td><td colspan="4"></td></tr>
<tr><td>Final report date</td><td colspan="4"></td></tr>
<tr><td rowspan="3">Demographic Data</td><td rowspan="2">No. of subjects</td><td>Enrolled</td><td>Completed</td><td>Withdrawal</td></tr>
<tr><td>--- male
--- female</td><td>--- male
--- female</td><td>Period I:
Period II:</td></tr>
<tr><td>Age (mean)</td><td colspan="3">---- years</td></tr>
<tr><td>Subjects</td><td colspan="3">Healthy
Other, specify,</td></tr>
</table>

<table>
<tr><td rowspan="5"></td><td>Average weight (mean)</td><td colspan="3"></td></tr>
<tr><td>Average height(mean)</td><td colspan="3"></td></tr>
<tr><td>Study condition</td><td colspan="3">Fast / Fed</td></tr>
<tr><td>wash-out period</td><td colspan="3">---- days (5 to 10 t half)</td></tr>
<tr><td>Sampling points</td><td colspan="3">0, 1, 2, 3
…….
hours
A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected
AUC(0-t) must cover at least 80% of AUC (0-∞)</td></tr>
<tr><td>Sample size satisfactory
(Should be based on an appropriate sample size)</td><td colspan="4"></td></tr>
<tr><td>Pharmacokinetics and Bioequivalence Parameters</td><td colspan="4">The following parameters were tested:
C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$.</td></tr>
<tr><td rowspan="2">Acceptance criteria based on study protocol</td><td>C_{max}</td><td>AUC_{0-t}</td><td>$AUC_{0-\infty}$</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Statistical methods/program</td><td colspan="3"></td></tr>
</table>

Pharmacokinetics

At least 2 QC sample levels should fall within the range of concentrations measured in study samples.	
No result below LLOQ in the volunteer's plasma concentration	
No result at time zero in the volunteer's plasma concentration.	
Cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if AUC (0-t) covers at least 80% of AUC (0-∞). N.B: not required in case of truncated design	
Frequent sampling around predicted tmax to provide a reliable estimate of peak exposure. Tmax:	
K elimination detailed calculation. (Time points selected for Kel should be fall into the elimination phase) N.B: not required in case of truncated design	
Table of individual subject pharmacokinetic parameters, descriptive statistics.	
Figure of mean plasma or urine concentration-time profile.	
Figure of individual subject plasma or urine concentration-time Profile.	

Pharmacokinetics Results Data **Active 1**						
Range	Test (T)			Reference (R)		
	Min	Max	Mean	Min	Max	Mean
C_{max} (ng/mL)						

AUC_{0-t}						
$AUC_{0-\infty}$						
t_{max}*			*			*
$t_{1/2e}$						
*Median						

Arithmetic mean	Test (T)	Reference (R)	T/R (%)
t_{max}			

Geometric Least-Squares Means (GLSM), Ratios and the 90% Confidence Interval

Parameters	GLSM Test (T)	GLSM Reference (R)	GLSM Ratio T/R (%)	90% Confidence Interval	
				Lower	Upper
ln C_{max}					
ln AUC_{0-t}					
ln $AUC_{0-\infty}$					

Public assessment reports and specific guidelines

Source of PARA	
Test product	
reference product	
Study design, Sampling times, washout period Are these data similar? If different, please specify	
Is there any FDA specific? recommendation?	

Bioanalytical method validation

Date of validation	
Calibration curve*: A minimum of six calibration concentration levels should be used, in addition to the blank sample (processed matrix sample without analyte and without IS) and a zero sample (processed matrix with IS). The back calculated concentrations of the calibration standards should be within ±15% of the nominal value, except for the LLOQ for which it should be within ±20% At least 75% of the calibration standards, with a minimum of six calibration standard levels, must fulfil this criterion*	
Linear range and concentrations	
Analyte	
Internal standard	
Selectivity: *Ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample. ≥6 sources of blank samples of the appropriate biological matrix (+1hemolytic, +1 lipemic) should be tested for interference, and selectivity should be ensured at the* *lower limit of quantification (LLOQ).*	

Acceptable limit: ≤20% of response at LLOQ and 5% for the internal standard.	
Matrix Effects in MS-based Assays *using at least 6 lots of blank matrix (+1 hemolytic, +1 lipemic) Matrix Factor; MF= measured by analyzing blank matrix spiked after extraction with Analyte), to the peak area in absence of matrix (pure solution of the Analyte). The IS normalized MF should also be calculated by dividing the MF of the analyte by the MF of the IS. The CV of the IS-normalized MF calculated from the 6 lots of matrix should not be greater than 15 %. This determination should be done at a low and at a high level of concentration (maximum of 3 times the LLOQ and close to the ULOQ)*	
Carry-over: *injecting blank samples after a high concentration sample or calibration standard at the* *upper limit of quantification Not greater than 20% of (LLOQ)*	
Lower limit of quantification *Should be not higher than 5% of the Cmax,*	
Accuracy: *assessed on samples spiked with known amounts of the QC samples.* Within-run accuracy*: should be determined by analyzing in a single run a minimum of 5 samples per level at a minimum of 4 concentration levels which are covering the calibration curve range:* *the LLOQ, within three times the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC). The mean concentration should be within 15% of the nominal values for the QC samples, except for the LLOQ which should be within 20% of the nominal value.* Between –run accuracy*: LLOQ, low, medium and high QC samples from at least three runs analyzed on at* *least two different days should be evaluated. The mean concentration should be within 15% of the*	

nominal values for the QC samples, except for the LLOQ which should be within 20% of the nominal value.	
Precision*: Describes the closeness of repeated individual measures* Within-run precision*: should be a minimum of five samples per concentration level at LLOQ, low, medium and high QC samples in a single run. The within-run CV value should not exceed 15% for the QC samples,* *except for the LLOQ which should not exceed 20%.* Between –run precision*: LLOQ, low, medium and high QC samples from at least three runs analyzed on at least two different days should be evaluated. The between-run CV value should not exceed 15% for the QC samples, except for the LLOQ which should not exceed 20%*	
Dilution integrity: *Dilution of samples should not affect the accuracy and precision. If applicable, dilution integrity should be demonstrated by spiking the matrix* *with an analyte concentration above the ULOQ and diluting this sample with blank matrix (at least five determinations per dilution factor). Accuracy and* *precision should be within the set criteria, i.e., within ±15%. Dilution integrity should cover the dilution applied to the study samples. Dilution integrity may be covered by partial validation*	
Stability: Freeze and thaw stability*: The QC samples are stored and frozen in the freezer at the intended temperature and thereafter thawed at room or processing temperature. After complete thawing, samples are refrozen again applying the same conditions. At each cycle, samples should be frozen for* *at least 12 hours before they are thawed.* *long term stability of the analyte in matrix stored in the freezer: The QC samples should be stored in the freezer under the same storage conditions*	

and at least for the same duration as the study samples.	
Average recovery of drug (%)	
Average recovery of IS (%)	
Bench-top stability (hours)	
Stock stability (days/ °C)	
Standard curve concentration (unit/ml)	
QC Intraday precision range (%)	
QC Intraday accuracy range (%)	
QC Interday precision range (%)	
QC Interday accuracy range (%)	
Anticoagulant used	
Certificate of reference standard (check purity)	

Bioanalytical method summary	

Analytical dates (start and end)	
Method description	
Analyte	
Linear range and concentrations	
Internal standard	
Standard curve concentration (unit/ml) HOQ MOQ LOQ LLOQ	
Period from first sample withdrawn in period one to the end of analysis (This period must be covered by long term stability study)	
Long term storage condition *(Must match long term stability study in validation)*	
Repeat analysis *(date, reasons for it in SOP and results)*	
Anticoagulant used	
Chromatograms for bioanalytical method	
20% of subject's chromatograms	
Incurred sample reanalysis *(Mandatory for studies that were conducted beyond 2013) The Difference between the two Values obtained should be within 20% of the Mean, for at least 67% of the Repeats. If no. of samples <1000 select 10% from the sample e.g., 700 x (10/100) If no. of samples >1000 select 10% from the first 1000 plus 50% from the exceeding.*	
Certificate of reference standard (check purity)	

Comparative dissolution profile summery

(In vivo- In vitro relation)

Information on the batches involved in dissolution *(the comparison should be between bio-batch and the reference used in the vivo study)*	☐ It is the bio-batch ☐ Another batch, please specify the size and the Type ------
Dissolution studies pH buffers	pH / Is provided? pH 1.2 ☒ pH 4.5 ☒ pH 6.8 ☒ QC ☒
Sampling time (Min/hour) A minimum of three time points (zero excluded)	Pass/ Fail
Dissolution protocol available:	Yes /No
Whether 85% of the drug dissolved within 15 min (very rapid)- [No need of Ƒ2 Value]	Yes /No / not applicable
If 85% of the drug dissolved within 30 min, (rapid) condition of at least three time points, first before 15min, second at 15min third point close to 85% --[No need of Ƒ2 Value]	Yes /No / not applicable
Are sampling time points same for the two formulations?	Yes /No Comment if any:

<table>
<tr><td>In case of F2 statistics not suitable, other alternatives justified</td><td>Yes /No Not applicable

Comment if any:</td></tr>
<tr><td>Tabular form (raw date) with all raw data of 12 dosage units available</td><td>Yes /No</td></tr>
<tr><td>Graphical representation of the test vs reference</td><td>Yes /No</td></tr>
<tr><td>The similarity factor f2 should be evaluated, if the f_2 value fall between 50 and 100 suggests that the two dissolution profiles are similar.</td><td>More than 85% was dissolved in 15 min for Dissolution media ----------
<table><tr><th>f2</th><th>Value</th></tr><tr><td>pH 1.2</td><td></td></tr><tr><td>pH 4.5</td><td></td></tr><tr><td>pH 6.8</td><td></td></tr><tr><td>QC media</td><td></td></tr></table></td></tr>
<tr><td>Dissolution studies specification</td><td><table><tr><th>specification</th><th>Value</th></tr><tr><td>Apparatus type</td><td></td></tr><tr><td></td><td></td></tr><tr><td>Speed</td><td>rpm</td></tr><tr><td>Volume</td><td></td></tr><tr><td>Temperature</td><td></td></tr><tr><td>No. of units</td><td></td></tr></table></td></tr>
</table>

	If the surfactant was used in the dissolution media, please specify the type and the concentration ----------
Relative Standard Deviations for the Results of the dissolution studies.	☐ RSD is below 20 % for the initial result ☐ RSD is below 10% for the remaining results

Appendix 2: Application Form

Request to Approve Contract Research Organization

☐ **New** ☐ **Renewal**

DSC/PV/GUD/001/FRM001/Vers.1

Section 1. Bioequivalence Center information

▪ Name			
▪ City			
▪ County			
▪ Postal code			
▪ Address			
▪ Telephone number			
▪ Website			
▪ Email address			
▪ Country of Origin approval date			
▪ Approval from Health Authorities	**Health Authorities**	**Approval date**	**Expiry date**
	☐ USFDA		
	☐ WHO		
	☐ Health Canada		
	☐ TGA		
	☐ EMA		
	☐ MHRA		
	☐ Not Applicable		
▪ Approval from other Health Authorities & Date of approval			

Section 2. Activities carried out/ out sourced by the CRO

***Mention the activities that are conducted by the CRO or Outsourced**

2.0.1 Clinical Phase

▪ Bioequivalence Center clinical analysis	☐ CRO ☐ Outsource
▪ Bioequivalence Center biochemistry laboratory	☐ CRO ☐ Outsource
▪ Bioequivalence Center hospital & clinics	☐ CRO ☐ Outsource

2.0.2 Analytical Phase

▪ Bioequivalence Center analytical Assays	☐ CRO ☐ Outsource
▪ Bioequivalence Center pharmacokinetic analysis	☐ CRO ☐ Outsource

2.0.3 Statistical Phase

▪ Bioequivalence Center statistical analysis	☐ CRO ☐ Outsource

2.1 Clinical Phase (Clinic for hospitalization)

▪ Name	
▪ Address	
▪ Telephone number	
▪ Email address	
▪ GPS	

2.2 Clinical Phase (Clinical Analysis Laboratory)

▪ Name	
▪ Address	
▪ Telephone number	
▪ Email address	
▪ GPS	

2.3 Analytical Phase (Analytical Assays)

▪ Name	
▪ Address	
▪ Telephone number	
▪ Email address	
▪ GPS	

2.4 Statistical Phase (Statistical Analysis)

▪ Name	
▪ Address	
▪ Telephone number	
▪ Email address	
▪ GPS	

Section 3: Other information

▪ Bioequivalence Center total area	
▪ Bioequivalence Center operational capacity	

▪ Bioequivalence Center biochemistry Laboratory total area	
▪ Bioequivalence Center clinical, analysis laboratory total area	
▪ Bioequivalence Center number of technicians	
▪ Bioequivalence Center area for hospitalization of subjects	
▪ Bioequivalence Center average number of tests	
▪ Bioequivalence Center number of technicians in clinical phase	
▪ Bioequivalence Center number of technicians in analytical phase	
▪ Buildings affiliated to the Bioequivalence Center (If any)	☐ Yes ☐ No Address**:**

Section 4: Attachments

▪ Bioequivalence Center CRO master file	
▪ Bioequivalence Center license issued by Health Authority	
▪ Bioequivalence Center inspection report issued by country of origin & Health Authorities in which the Center is approved. (Full Inspection Report)	
▪ GLP & GCP certificates	
▪ Last inspection report by MOH, Oman (For renewal application, if available)	