INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS M13A

Draft version

Endorsed on 20 December 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

M13A
Document History

Code	History	Date
M13A	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation.	20 December 2022

ICH HARMONISED GUIDELINE

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

M13A

ICH Consensus Guideline

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Objective

This guideline is intended to provide recommendations on conducting bioequivalence (BE) studies during both development and post approval phases for orally administered immediate-release (IR) solid oral 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(ies) when an alternate approach is proposed or taken.

1.2 Background

1.2.1 Bioequivalence

BE for IR solid oral dosage forms with systemic action is largely established via clinical pharmacokinetic (PK) BE studies or comparative *in vitro* dissolution studies. In addition to the oral dosage forms stated above, the PK principles of this guideline are generally applicable to non-orally administered drug products with immediate action in which reliance on systemic exposure measures is suitable for establishing BE, e.g., certain rectal, inhalation, and nasal drug products.

BE assessment for these oral dosage forms is important for establishing therapeutic equivalence for generic drug products to their respective comparator products. In addition, there may be situations in new (innovator) drug development when demonstration of BE may be critical for approval decisions. Furthermore, BE studies are used by innovator and generic product developers for supporting post-approval formulation and/or manufacturing process changes.

Two drug products containing the same drug substance(s) are considered bioequivalent if their relative bioavailability (BA) (rate and extent of drug absorption) after administration in the same molar dose lies within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e., similarity in terms of safety and efficacy.

The Biopharmaceutics Classification System (BCS)-based biowaiver may be used to waive *in vivo* BE studies for certain orally administered IR solid oral dosage forms as delineated in ICH M9,

Biopharmaceutics Classification System-Based Biowaivers.

1.2.2 Data Integrity

BE studies should be conducted according to the principles and recommendations in ICH E6, *Good Clinical Practice*. In conducting BE studies, sponsors, study investigators, and service providers, e.g., contract research organisations or laboratories, should ensure that the data generated are attributable, legible, contemporaneously documented, original (or a certified copy), accurate, complete, and traceable. The ultimate responsibility for the quality and integrity of the study data submitted to a regulatory authority lies with the applicant.

1.3 Scope

M13A is the first guideline in the series to describe the scientific and technical aspects of study design and data analysis to support BE assessment for orally administered IR solid oral dosage forms. How regulatory decisions may be made based on BE assessment is out of the scope of this guideline.

Acceptance of comparator products across regulatory jurisdictions could reduce the burden of multiple clinical trials demonstrating BE against local comparator products. However, in many regions this is governed by local laws rather than scientific guidelines. Therefore, the acceptance of comparator products across regions is not in the scope of M13A. However, study designs containing multiple comparator products or test products are included in M13A to take some initial steps to reduce the associated burden without prejudice to regional legal requirements.

The second guideline in the series, M13B, will describe biowaiver considerations for additional strengths not investigated in BE studies.

The third guideline in the series, M13C, will include data analysis and BE assessment for 1) highly variable drugs, 2) drugs with narrow therapeutic index, and 3) complex BE study design and data analysis considerations, e.g., adaptive BE study design.

These guidelines do not cover PK study design or data analysis to support BA assessment for new drug development in support of intended use or dosing recommendations in drug labelling, e.g., relative BA assessment, food effect, drug-drug interactions, special population studies, bridging

formulations without the necessity to demonstrate BE, and studies to support changes in dosing regimens or routes of administration. In such cases, study design and decision criteria may be based on the objective of the study and availability of other information including exposure-response and proposed labelling.

2 GENERAL PRINCIPLES IN ESTABLISHING BIOEQUIVALENCE

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies

2.1.1 Study Population

The subject population for BE studies should be selected with the aim of permitting detection of differences in the *in vivo* release characteristics between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical. Conducting BE studies in healthy subjects is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended.

The subject inclusion and exclusion criteria should be clearly stated in the study protocol. Subjects should be at least 18 years of age and preferably have a Body Mass Index between 18.5 and 30.0 kg/m^2. If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects.

Subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination. Depending on the drug's therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during, and after the completion of the BE study. The risk to women of childbearing potential should be considered, and the investigators should ensure that female subjects are not pregnant or lactating during the BE study and the follow-up. Subjects should preferably be non-nicotine users and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or PK reasons.

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy subjects, the study may instead be

conducted in a targeted patient population under suitable precautions and supervision.

2.1.2 Study Design

A randomised, single-dose, two-period, two-sequence crossover study design is recommended when comparing two formulations, as single-dose studies provide the most sensitive conditions to detect differences in the rate and extent of absorption. Treatment periods should be separated by a sufficiently long washout period, e.g., at least 5 elimination half-lives. In general, the highest to-be-marketed strength should be used in a BE study. If the highest strength of a product cannot be administered to healthy subjects for safety and/or tolerability reasons, a single-dose study conducted in healthy subjects using a lower strength may be possible (see Section 2.1.6) or alternatively, if feasible given the drug product under investigation, a single-dose study conducted in patients using the highest proposed strength could be considered.

A multiple-dose study may be conducted in patients if a single-dose study cannot be conducted in either healthy subjects for safety and/or tolerability reasons or in patients for ethical reasons. For a multiple-dose study, the study protocol should include an appropriate number of dosage administrations to reach steady-state, which could be justified using an appropriate sampling scheme, i.e., concentrations at the end of the dosing interval should be sampled sequentially until C_{tau} is stable. The washout of the last dose of the first treatment period can overlap with the accumulation of the second treatment. The accumulation period should be sufficiently long to reach the new steady-state after switching and allow the elimination of the drug from the previous treatment, e.g., at least 5 elimination half-lives.

For drugs with long elimination half-lives, a parallel design may be employed when a crossover design is impractical due to the need for a prolonged washout period. In this situation, special care should be taken to ensure similar subject demographics in each of the treatment groups.

Alternative study designs are acceptable, if scientifically justified.

2.1.3 Sample Size for Bioequivalence Studies

The number of subjects to be included in the BE study should be based on an appropriate sample size calculation to achieve a pre-specified power and pre-specified type 1 error. A sufficient number of subjects should be enrolled in the BE study to account for possible dropouts and/or

withdrawals. The use of "spare" subjects is not acceptable. Additional cohort(s) of subjects may be added to the study, e.g., if the number of evaluable subjects falls below the calculated sample size; however, this should be specified in the study protocol and done prior to any bioanalysis. The number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover design or 12 per treatment group for a parallel design.

2.1.4 Comparator and Test Products

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.

The selection of the batch of the comparator product used in the BE study should be based on assay content. It is advisable to investigate more than one batch of the comparator product when selecting the batch of comparator product for use in the BE study.

The test product used in the BE study should be representative of the product to be marketed and this should be discussed and justified by the applicant.

For pivotal BE studies, the test product used should meet the following criteria:

a) The production of batches used should provide a high level of assurance that the product and process will be feasible on a commercial scale. 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 smaller than 100,000 units, a full production batch is required.
b) Unless otherwise justified, the assayed content of the batch used as test product should not differ by more than 5% from that of the batch used as comparator product, as determined with the test procedure proposed for routine quality testing of the test product.

2.1.5 Fasting and Fed Study Conditions

BE studies should be conducted under standardised conditions that minimise variability to better detect potential PK differences between drug products. For IR solid oral dosage forms, single-dose BE studies conducted under fasting conditions typically provide greater discrimination between the PK profiles of two products. Therefore, for the majority of these drug products, BE may be demonstrated in a single study conducted under fasting conditions.

However, food can have a differential, formulation-dependent impact on the absorption of drug substances from drug products that are of high risk (see "High-risk products" section below), which would preclude the extrapolation of BE under fasting conditions to fed conditions. In such cases, BE under fed conditions also needs to be demonstrated.

The design of a BE study with regard to the use of fasting and/or fed conditions depends on the dosing instructions of the comparator product as well as the properties of the drug substance and product formulation. A rationale should be provided for the selection of the type of BE study(ies) (fasting or fed or both) and meal type, e.g., fat and calorie content, based on the understanding of the comparator product and the test product (high or non-high risk) as described below. The rationale can be supported by modelling, e.g., appropriately validated/qualified physiologically-based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models.

In addition, safety-related aspects need to be considered when selecting the appropriate condition for a BE study regarding food intake. If safety concerns make it unethical to administer a single dose of the drug product under either fed or fasted conditions, the BE study should be conducted under the condition with less safety concerns.

For non-high-risk products, the following is recommended:

- For a product that is labelled to be taken only under fasting conditions or can be taken under fasting or fed conditions i.e., without regard to food, a single BE study conducted under fasting conditions is recommended to demonstrate bioequivalence.
- For a product that is labelled to be taken only with food due to PK reasons, e.g., enhancing absorption or reducing variability, a single BE study conducted under fed conditions is recommended to demonstrate bioequivalence.
- For a product that is labelled to be taken only with food due to tolerability reasons, e.g., stomach irritation, a single BE study conducted under either fasting or fed conditions is acceptable.

<u>High-risk products:</u>

High-risk products are those where the complexity of the formulation design or manufacturing process leads to an increased likelihood that *in vivo* performance will be impacted differently by

varying gastrointestinal (GI) conditions between the fasted and fed states. For these products, performance differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be conducted. For example, some drug products containing low solubility drug substances (as defined by the BCS low solubility criterion described in ICH M9) have complex formulation and/or manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies) to ensure sufficient solubility of the drug substance and dissolution of the drug products or to manage the impact of food. For these high-risk products, BE studies should be conducted under both fasting and fed conditions, irrespective of the product labelling with regard to food intake, except when safety concerns make it unethical to administer a single dose of the drug product under either fed or fasted conditions. Then the BE study should be conducted under the condition with less safety concerns.

Especially for low solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect. If the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this may warrant the need for BE studies under fasting and fed conditions.

The above principles with regard to fasting and fed study conditions also apply when BE studies are deemed necessary to bridge formulation and/or manufacturing process changes during pre- or post-marketing phases.

Standardisation with regard to meals and water:

For studies conducted under fasting conditions, subjects should be fasted for at least 10 hours before drug administration. Subjects should be allowed water as desired, except for 1 hour before and 1 hour after drug administration. The dose should be administered with a standardised volume of water, in the range of 150 to 250 millilitres (ml). No food should be allowed for at least 4 hours post-dose on each day of drug administration and meals taken should be standardised with respect

to composition and timing.

In the case of studies conducted under fed conditions, the same controls should be employed with the exception that a pre-dose meal should be provided. For a fed BE study, it is recommended that subjects start the meal 30 minutes before administration of the drug product and consume the meal within 30 minutes.

If BE studies are conducted under both fasting and fed conditions, i.e., for high-risk products, the BE study conducted under fed conditions should be conducted using a meal that has the potential to cause the greatest effect on GI physiology. The meal should be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal, which should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. It is recognised that there may be situations where it is appropriate to administer a pre-dose meal with a different caloric/fat content from these recommendations, e.g., for studies performed in patient populations who cannot tolerate the recommended meal composition.

If, however, only one BE study conducted under fed conditions is needed for a non-high-risk product, either a high-fat, high-calorie meal or a low-fat, low-calorie meal, e.g., a meal of approximately 500 kcal with approximately 25% of calories from fat, may be administered. If the type of meal to be consumed at the time of drug product administration is clearly specified in the comparator product labelling, then this meal should be employed in the BE study.

The composition of the meal to be administered should be described with regard to protein, carbohydrate, and fat content (specified in grams, kcal, and relative caloric content (%)) in the study protocol.

In all situations, subjects should abstain from foods and drinks that may interact with circulatory, GI transporter, GI enzymatic, hepatic, or renal function, e.g., alcoholic or caffeinated drinks, or certain fruit juices such as grapefruit juice, during a suitable period before and during the study.

2.1.6 Dose or Strength to be Studied

In case of an application with multiple strengths, the strength to be used in the BE study depends on the dose proportionality in PK and solubility of the analyte. Generally, the highest to-be-marketed strength can be administered as a single unit. Selection of a lower strength may also be

accepted if the highest strength cannot be administered to healthy subjects for safety and/or tolerability reasons and dose proportional PK, i.e., area under the concentration vs time curve (AUC) and C_{max}, has been documented over the range of strengths. If warranted to achieve sufficient bioanalytical sensitivity, multiple units of the highest strength can be administered, provided the total single-dose remains within the labelled dose range and the total dose is safe for administration to the study subjects.

For non-proportional increases in AUC and/or C_{max} with increased dose there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. To assess dose proportionality, the applicant should consider all available data regarding dose proportionality. Assessment of dose proportionality should consider single-dose studies only.

For drugs with a more than proportional increase in AUC and/or C_{max} with increasing dose over the therapeutic dose range, the BE study should in general be conducted at the highest strength.

For drugs with a less than proportional increase in AUC and/or C_{max} with increasing dose over the therapeutic dose range, BE should be established at the lowest strength if this situation is due to saturation of absorption. If the less than proportional increase in AUC and/or C_{max} with increasing dose is due to limited drug solubility, BE studies should be conducted at both the lowest and highest strengths. If the reason for non-dose proportionality is unknown, BE studies should generally be conducted at both the lowest and highest strengths.

2.1.7 Moieties to be Measured

2.1.7.1 Parent versus Metabolite

Demonstration of BE should be based on the analysis of the parent drug because the concentration-time profile of the parent drug is usually considered more sensitive to detect a difference between formulations than metabolite data. This also applies to prodrugs. However, some prodrugs are rapidly eliminated resulting in difficulties in demonstrating BE based on parent drug data, because the parent drug levels are too low to allow reliable bioanalytical measurement. In this situation, it is acceptable to demonstrate BE based on a primary metabolite, i.e., a first-step metabolite of the parent drug, without measurement of the parent compound.

In rare cases, demonstration of BE based on the parent drug alone may not be sufficient and the

primary active metabolite should also be considered, e.g., drugs that have metabolites formed through gut wall or gut lumen metabolism that contribute to efficacy or safety. This is intended to address situations in which the formation of the metabolite could be influenced by formulation differences, which may not be detectable when measuring systemic levels of the parent drug.

2.1.7.2 Enantiomers versus Racemates

The use of an achiral bioanalytical assay to measure the racemate is generally acceptable. However, a stereoselective assay measuring individual enantiomers in BE studies should be employed when it is known that all of the following conditions have been met:

a) the enantiomers exhibit different pharmacodynamic properties,
b) the enantiomers exhibit different PK properties, and
c) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

It is sufficient to demonstrate BE for only the active enantiomer in cases where one enantiomer is inactive (or makes a low contribution) with respect to both safety and efficacy.

2.1.8 Sampling

The sampling schedule in a BE study should cover the concentration-time curve, including a pre-dose sample, samples in the absorption phase, frequent samples around the expected T_{max}, and sufficient samples after T_{max} to ensure a reliable estimate of the extent of exposure, which is achieved when $AUC_{(0\text{-}t)}$ covers at least 80% of $AUC_{(0\text{-}inf)}$. This period is usually at least three times the terminal half-life of the drug, unless a suitable truncated AUC, e.g., $AUC_{(0\text{-}72h)}$, is used. To permit calculation of the relevant PK parameters, a sufficient number of samples should be collected per subject per period, distributed across all phases of disposition.

The exact times at which the samples are taken should be recorded to obtain the elapsed time relative to drug administration and sampling should be spaced such that C_{max}, $AUC_{(0\text{-}t)}$, and k_{el} can be estimated accurately.

There may be considerable inaccuracies in the estimates of k_{el} if the constant is estimated from linear regression based on a small number of data points. To reduce these inaccuracies, it is recommended that three or more data points in the terminal log-linear phase of the concentration-

time curve be used to estimate k_{el}.

In multiple-dose studies, the pre-dose sample should be taken immediately before dosing, i.e., within 5 minutes of dosing, and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0\text{-}tauSS)}$.

2.1.8.1 First Point C_{max}

The sampling schedule should include frequent sampling around the anticipated T_{max} to provide a reliable estimate of C_{max}. In particular, the occurrence of C_{max} at the first post-dose sampling time point should be avoided by careful consideration of the known pharmacokinetic properties of the drug and selection of a suitable early sampling schedule. Datasets where C_{max} occurs at the first post-dose sampling time may result in exclusion of the data from affected subjects from the analysis.

2.1.8.2 Long Half-life Drugs and Truncated AUC Considerations

Truncating AUC for orally administered IR drug products known to exhibit longer elimination half-lives, i.e., 24 hours or longer, mitigates the clinical challenge of prolonged sampling and follow-up. For such products, $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparison of the extent of absorption. Seventy-two hours is considered to be adequate to ensure completion of GI transit of the drug product and absorption of the drug substance.

2.1.8.3 Early Exposure

For orally administered IR drug products, BE can generally be demonstrated by measurement of rate and extent of absorption, i.e., C_{max} and $AUC_{(0\text{-}t)}$. However, in some situations, C_{max} and $AUC_{(0\text{-}t)}$ may be insufficient to adequately assess the BE between two products, e.g., when the early onset of action is clinically relevant. In these cases, an additional PK parameter, such as area under the concentration vs. time curve between two specific time points (pAUC), may be applied. This pAUC is typically evaluated from the time of drug administration until a predetermined time-point that is related to a clinically relevant pharmacodynamic measure. Samples should be spaced such that the pAUC can be estimated accurately.

2.2 Data Analysis for Non-Replicate Study Design

2.2.1 Considerations for the Bioequivalence Analysis Population

It is imperative that all criteria for study subject inclusion into the BE analysis population be clearly defined in the study protocol. Any exclusions from the BE analysis population should be documented prior to bioanalytical analysis, e.g., subjects that are withdrawn from the study, have protocol violations, or experience GI disturbances potentially affecting absorption.

2.2.1.1 Removal of Data Due to Low Exposure

BE studies are studies with a smaller number of subjects compared to other clinical trials. An extreme value in the dataset can have a large impact on the outcome of the BE study. Although statistical tests may identify extreme values in the PK variables, such data should not be removed from the statistical analysis of BE studies solely on this basis. Data should only be removed from the statistical analysis based on protocol violations which are contemporaneously documented. A prospective plan should be included in the study protocol for removing data from the BE statistical analysis.

An exception to the above can be made for a subject without measurable concentrations or only very low concentrations following either comparator or test product administration. A subject is considered to have very low concentrations if the AUC for that period is less than 5% of the geometric mean AUC of the product in question, which should be calculated without inclusion of data from the subject. These very low concentrations are considered the result of subject non-compliance and should, as far as possible, be avoided by documenting mouth check of subjects after administration of study medication to ensure the subjects have swallowed the drug product. The exclusion of data for this reason will only be accepted in exceptional cases (in general with no more than 1 subject in each study) and may bring the reliability of dose administration into question.

Data from redosing studies are not considered evidence to support removal of extreme values from the statistical analysis.

Note that all subject data should be submitted and potential extreme values flagged with appropriate documentation as part of the application.

2.2.2 Presentation of Data

2.2.2.1 Concentration Time Data

For both the test and comparator products, the drug concentration in a suitable biological fluid, e.g., plasma, serum or blood, determined at each sampling time point should be tabulated for each subject participating in the study, along with descriptive statistics. These data should be presented on the original scale, i.e., as unadjusted, measured drug concentrations. Deviations from the protocol, e.g., missed samples or samples with significant time deviation, should be clearly identified. Drug concentrations in study samples should be measured in accordance with ICH M10, *Bioanalytical Method Validation and Study Sample Analysis*.

Two concentration-time graphs (linear and log-linear) should be provided for both the test and comparator products for each individual subject. In addition, two concentration-time graphs (linear and log-linear) should be provided for both the test and comparator products for the mean drug concentrations of all subjects. For the individual subject concentration-time graphs, the drug concentrations should be plotted against time using the actual sampling times. For the mean concentration-time graphs the drug concentrations should be plotted using the nominal sampling times.

2.2.2.2 Pharmacokinetic Analysis

For single-dose studies, the following PK parameters should be tabulated for each subject-formulation combination: 1) primary parameters for analysis: $AUC_{(0\text{-}t)}$, C_{max}, and, where applicable, pAUC, and 2) additional parameters for analysis to assess the acceptability of the bioequivalence study: $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}$, T_{max}, k_{el}, and $t_{1/2}$. For single-dose studies, $AUC_{(0\text{-}t)}$ should cover at least 80% of $AUC_{(0\text{-}inf)}$. If the $AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}$ percentage is less than 80% in more than 20% of the observations, then the validity of the study may need to be discussed in the submission. If the AUC is truncated at 72 hours for long half-life drugs, the primary AUC parameter for analysis is $AUC_{(0\text{-}72h)}$ and the following additional parameters are not required: $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}$, k_{el}, and $t_{1/2}$.

Summary statistics to be reported include geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, number of observations, minimum, and maximum. Each

variable should be computed using the actual time of sampling for each concentration data point. The non-compartmental methods used to derive the PK parameters from the raw data should be reported, e.g., linear trapezoidal method for AUC and the number of data points of the terminal log-linear phase used to estimate the terminal elimination rate constant (k_{el}).

For multiple-dose studies, applicants should document appropriate dosage administration and sampling to demonstrate the attainment of steady-state. For steady-state studies, the following PK parameters should be tabulated: 1) primary parameters for analysis: C_{maxSS} and $AUC_{(0\text{-}tauSS)}$, and 2) additional parameters for analysis: C_{tauSS}, C_{minSS}, C_{avSS}, degree of fluctuation, swing, and T_{max}.

Any concentration reported as below the lower limit of quantification (LLOQ) should be treated as zero in PK parameter calculations. Values below the LLOQ are to be omitted from the calculation of K_{el} and $t_{1/2}$.

2.2.2.3 Potency Differences in Lots

The results from the potency assay of the test and comparator products should be submitted and the test product batch should be within 5% of the comparator product batch. In exceptional cases where a comparator product batch with a measured drug content within 5% of a test product batch cannot be obtained, a potency correction may be accepted with supporting justification, e.g., potency data from multiple lots of comparator product, pending market availability, and considering the totality of evidence. If potency correction is to be used, this intention should be pre-specified in the study protocol. Analysis should be provided for both uncorrected data and for potency-corrected data. If the potency correction is justifiable, the applicable BE standards should be met on potency-corrected data.

2.2.3 Statistical Analysis

2.2.3.1 General Considerations

The statistical analyses should include all data for all subjects who provide evaluable data for the products being compared. Decisions made to exclude subjects from the BE analysis population, e.g., due to incomplete sampling or protocol violation, should be documented at the end of the clinical blood sampling portion of the study and prior to subject sample analysis. A study will not be considered acceptable if there are fewer than 12 evaluable subjects for a crossover analysis or

for each treatment arm for a parallel analysis.

The assessment of BE is based on 90% confidence intervals for the geometric mean ratios (test/comparator) for the primary PK parameters under consideration. This method is equivalent to two one-sided t-tests with the null hypotheses of bioinequivalence at the 5% significance level. The data should be transformed prior to analysis using a logarithmic transformation.

The model to be used for the analysis should be pre-specified in the study protocol. The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable.

The report on the data analysis should be sufficiently detailed to enable the PK and the statistical analyses to be repeated, e.g., data on actual time of blood sampling after dose, drug concentrations, the values of the PK parameters for each subject in each period, and the randomisation scheme should be provided.

2.2.3.2 Crossover Design Studies

Conventional two-treatment, two-period, two-sequence randomised crossover design studies should be analysed using an appropriate parametric method, e.g., ANOVA. The tables resulting from such analyses including the appropriate statistical tests of all effects in the model should be submitted, e.g., a summary of the testing of Sequence, Subject within Sequence, Period, and Formulation effects should be presented. In general, the primary analyses should include all data for all subjects who provide evaluable data for both the test and comparator products.

2.2.3.3 Carry-over

A test for carry-over is not considered relevant and no decisions regarding the analysis, e.g., analysis of the first period only, should be made on the basis of such a test. In crossover studies, the potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 and beyond if applicable, e.g., period 3 in a 3-period study.

If there are subjects for whom the pre-dose concentration is greater than 5% of the C_{max} value for the subject in that period, then the pivotal statistical analysis should be performed excluding the data from that subject.

2.2.3.4 Parallel Design Studies

The statistical analysis for parallel design studies should reflect independent samples. Demographic characteristics or other relevant covariates known to affect the PK should be balanced across groups, to the extent possible. The use of stratification in the randomisation procedure based on a limited number of known relevant factors is therefore recommended. Those factors are also recommended to be accounted for in the pre-defined primary statistical analysis. Post hoc and data-driven adjustments are not acceptable for the primary statistical analysis.

2.2.3.5 Multi-Group Design Studies

Sample size requirements and/or study logistics may necessitate studies to be conducted with groups of subjects. The BE study should be designed to minimise the group effect in the study. The combination of multiple factors may complicate the designation of group.

BE should be determined based on the overall treatment effect in the whole study population. In general, the assessment of BE in the whole study population should be done without including the Group by Treatment interaction term in the model, but applicants may also use other pre-specified models, as appropriate. However, the appropriateness of the statistical model should be evaluated to account for the multi-group nature of the BE study. Applicants should evaluate potential for heterogeneity of treatment effect across groups, i.e., Group by Treatment interaction. If the Group by Treatment interaction is significant, this should be reported and the root cause of the Group by Treatment interaction should be investigated to the extent possible. Substantial differences in the treatment effect for PK parameters across groups should be evaluated. Further analysis and interpretation may be warranted in case heterogeneity across groups is observed.

In multicentre BE studies, when there are very few subjects in some sites, these subjects may be pooled into one group for consideration in the statistical analysis. Rules for pooling subjects into one group should be pre-specified and a sensitivity analysis is recommended.

Statistical methods and models should be fully pre-specified. Data-driven post hoc analysis is highly discouraged but could be considered only in very rare cases where a very robust scientific justification is provided.

2.2.4 Bioequivalence Criteria

For the majority of drug products, the PK parameters to demonstrate BE include C_{max} and $AUC_{(0-t)}$.

For drugs with a long elimination half-life, $AUC_{(0-72h)}$ may be used in place of $AUC_{(0-t)}$ (see Section 2.1.8.2). For drugs where it is clinically relevant to assess the early exposure or early onset of action, an additional PK parameter, pAUC, may be used to establish BE (see Section 2.1.8.3).

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%.

2.2.5 Multiple Comparator and Multiple Test Product Studies

2.2.5.1 Multiple Comparator Products

It may be necessary to demonstrate BE between a test product and multiple comparator products to meet requirements from multiple jurisdictions. In such case, including comparator products from different regions in one trial is acceptable to streamline the BE demonstration by conducting one single higher-order crossover BE study with multiple comparator products.

Although there are multiple comparator products tested, multiplicity correction, i.e., alpha adjustment, is not needed because comparator products are considered independent and region-specific. Decisions will be made independently about a test product relative to a single comparator product within a single jurisdiction. It is preferred for the statistical analysis to only test two at a time and not all at once, making pairwise comparison within the analysis.

It is possible that the results meet the BE acceptance criteria with one region-specific comparator product but not meet BE acceptance criteria with the other region-specific comparator product. In such case, BE is demonstrated with one comparator product and not demonstrated with the other comparator product. The protocol should specify the main objectives of the study and which comparisons are to be performed.

Complete study results from all comparisons performed should be included in the clinical study report.

2.2.5.2 Multiple Test Products

It may be necessary to demonstrate BE between multiple test products and the comparator product,

e.g., in order to include different test formulations that may be required due to drug development needs. To streamline the demonstration of BE, it is permitted to conduct one single crossover BE study with multiple test products.

The need to apply multiplicity correction in pivotal trials depends on the underlying objectives of the trial:

a) If the objective is to achieve BE for all test formulations versus the comparator product, then no alpha adjustment is needed.
b) If the objective is to show BE for any of the test formulations, then multiplicity adjustment may be needed.

The objective of the trial and method for multiplicity correction should be pre-specified in the study protocol.

3 SPECIFIC TOPICS

3.1 Endogenous Compounds

As endogenous compounds are identical to the drug that is being administered it can be challenging to determine the amount of drug released from the dosage form and absorbed for BE assessment. Therefore, in most cases, it is important to measure the baseline endogenous concentrations in biological matrices, e.g., blood, plasma, or urine, and subtract these concentrations from the total concentrations measured from each subject after the drug product is administered.

When the endogenous concentrations are influenced by diet, restricting or standardising the dietary intake of the substance before and during the study should be considered.

The exact method for baseline correction should be pre-specified and justified in the study protocol. Multiple baseline endogenous concentrations should be measured from each subject in the time period before administration of the study drug. The time-averaged baseline or time-matched baseline concentrations are subtracted from post-dose concentrations for those subjects in an appropriate manner consistent with the PK properties of the drug. For the time-averaged method, either the mean or median value may be used.

Baseline concentrations should be determined for each period and baseline correction should be period specific. It should be ensured that the washout period is of an adequate duration because carry-over effects cannot be readily detected. If a baseline correction results in a negative concentration value, the value should be set equal to zero.

PK and statistical analyses should be performed on both baseline uncorrected and baseline corrected data. In general, determination of BE should be based on the baseline corrected data.

Alternatively, the need for baseline correction may be avoided by enrolling study subjects with low or no production of the endogenous compounds.

3.2 Other Immediate-Release Dosage Forms

3.2.1 Orally Disintegrating Tablets

Orally Disintegrating Tablets (ODTs) should be administered in BE studies according to the comparator product labelling with regard to intake of water.

If the comparator product labelling states that the ODT can be taken with or without water, the test and comparator products should be administered in the BE study without water, as this is considered to be the more discriminating scenario. BE of the test and comparator ODT products taken with water can then be inferred.

For new intended label use/instructions, e.g., ODT as an extension to another orally administered IR drug product, BE studies may be conducted to determine whether the ODT is BE to the comparator product. In this scenario, the ODT product should be administered according to its intended labelling and compared with the comparator product administered as per its labelling.

If the new intended label use/instructions states that the ODT can be taken with or without water, a 3-arm BE study is recommended to determine BE of the ODT administered with and without water compared to the comparator product administered as per its labelling.

In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing a small amount of water, e.g., 20 ml, directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as orodispersible films, buccal tablets or films, and sublingual tablets may be handled in a similar way to that described above for ODTs.

3.2.2 Chewable Tablets

Chewable tablets should be administered in BE studies according to the comparator product labelling with regard to intake of water.

If the comparator product labelling states that the chewable tablets can be taken with or without water, the test and comparator products should be administered in the BE study without water, as this is considered to be the more discriminating scenario. BE of the test and comparator chewable tablet products taken with water can then be inferred.

For new intended label use/instructions, e.g., chewable tablets as an extension to another orally administered IR drug product, BE studies may be conducted to determine whether the chewable tablet is BE to the comparator product. In this scenario, the chewable tablet product should be administered according to its intended labelling and compared with the comparator product administered as per its labelling.

If the new intended label use/instructions state that the chewable tablets can be taken with or without water, a 3-arm BE study is recommended to determine BE of the chewable tablets administered with and without water compared to the comparator product administered as per its labelling.

3.2.3 Oral Suspensions

For tablets, granules, and powders labelled as being only intended to be dispersed in a liquid before administration as an oral suspension, BE studies should be conducted according to the comparator product labelling.

For new intended label use/instructions (not included in the comparator product labelling), the test product should be administered according to its intended labelling and compared with the comparator product administered as per its labelling.

3.3 Fixed Dose Combination

The BE study design for fixed-dose combination products should follow the principles described

in this guideline. BE should be determined using a PK sampling scheme suitable for the determination of the PK parameters of the individual components (drugs) and employing bioanalytical methods validated for the determination of the individual drugs in the presence of the other component(s) in the combination product. PK parameters to be assessed and reported are those that would normally be required for each drug if it were in the formulation as a single entity. BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline. Failure to demonstrate BE for one component of the fixed-dose combination results in failure to demonstrate BE for the proposed fixed-dose combination product as a whole.

3.4 pH-Dependency

The absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH. This impact on drug absorption can be altered due to the use of, for instance, pH stabilising excipients or a specific salt-form in the formulation. Moreover, the formulation of the final marketed comparator product may be the result of an extensive formulation development program, obtaining for instance a specific formulation without an effect on drug absorption due to gastric pH differences. This is especially relevant in cases where it is foreseen that the product will be taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used in certain populations, e.g., patients with achlorhydria. Therefore when, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility, BE under normal fasting conditions between the two products may not ensure BE of the two products in a gastric pH-altered situation, e.g., in the presence of a pH-modifying drug product. In such a situation, an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE.

Applicants may provide a scientific justification to demonstrate that a BE study in a gastric pH-altered situation may not be needed. Such a justification should be based on the totality of evidence referring to the pH-solubility profile of the drug substance, impact of excipients, formulation and manufacturing design, e.g., formulation designed to overcome pH effects, extent of the differences between the test and comparator products, and comparative dissolution testing at multiple pHs. Modelling, e.g., appropriately validated/qualified PBPK modelling or semi-mechanistic

absorption models, and virtual BE simulation may be used to further assess the risk of bioinequivalence.

4 DOCUMENTATION

The report of the BE study should include the complete documentation of its protocol, conduct, and evaluation. It should be written in accordance with ICH E3, *Structure and Content of Clinical Study Reports*.

Names and affiliations of the responsible investigator(s), the site of the study, and the period of its execution should be stated.

Listing of inspection history for BE studies conducted at the relevant clinical and bioanalytical site(s) for the 5 years preceding completion of the study should also be provided in the study report (but may alternatively be provided elsewhere in the Common Technical Document (CTD)).

Comparator product name, strength, pharmaceutical form, batch number, manufacturer, expiration date, and country of purchase should be stated.

Certificates of analysis, or equivalent documents, of comparator and test batches used in the study should be included in an appendix to the study report.

The identity of the of the test product(s) used in the study should be provided, i.e., pharmaceutical form, strength, batch number, and measured content (% of label claim). The batch size, manufacturing date (and, if available, the expiry date) as well as the qualitative and quantitative composition of the test product should also be indicated (but may alternatively be provided elsewhere in the CTD).

Concentrations and PK data and statistical analyses should be presented in the level of detail described in this guideline (see Section 2.2). The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

Information on bioanalytical method validation and study sample analysis according to ICH M10 should be included in the appropriate section of Module 5 of the CTD.

The data generated should be properly documented and available for audit and inspection. Essential documents should be archived in accordance with ICH E6 and applicable regulatory requirements.

Data in a suitable electronic format should be submitted to enable the PK and the statistical analyses to be repeated, e.g., data on actual times of blood sampling, drug concentrations, the values of the PK parameters for each subject in each period, and the randomisation scheme.

Module 2.7.1 of the CTD should list all relevant BE studies conducted regardless of the study outcome. Full study reports should be provided for the BE study(ies) upon which the applicant relies for approval. For all other studies, synopses of the study reports (in accordance with ICH E3) are sufficient. However, complete study reports for these studies should be available upon request.

5 GLOSSARY

Applicant:

The entity submitting the application for marketing authorisation to the relevant regulatory authority.

AUC:

Area under the concentration vs. time curve

AUC $_{(0\text{-}inf)}$:

Area under the concentration vs. time curve extrapolated to infinity

AUC $_{(0\text{-}t)}$:

Area under the concentration vs. time curve from time zero to the time of last quantifiable concentration

AUC $_{(0\text{-}tauSS)}$:

Area under the concentration vs. time curve for one dosing interval at steady state

$AUC_{(0\text{-}72h)}$:

Area under the concentration vs. time curve from time 0 to 72 hours

Batch (or Lot):

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

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.

C_{avSS}:

Average concentration observed during dosing interval at steady state ($AUC_{0\text{-}tau}$/tau)

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.

C_{max}:

Maximum concentration after dosing

C_{maxSS}:

Maximum concentration observed during dosing interval at steady state

C_{minSS}:

Minimum concentration observed during dosing interval at steady state

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 guidance, 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.

C_{tau}:

Concentration observed at end of dosing interval

C_{tauSS}:

Concentration observed at end of dosing interval at steady state

Enantiomers:

Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable 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.

Fluctuation:

$[(C_{maxSS}-C_{minSS}) / C_{avSS}]$

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.

kcal:

A unit used to describe amount of energy in relation to food or energy burned with exercise. When it comes to nutrition and exercise, kilocalories (kcal) and calories equal the same amount of energy. One kcal (kilocalorie) equals 1 calorie in nutrition.

k_{el}:

The apparent terminal elimination rate constant 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.

pAUC:

Area under the concentration vs. time curve between two specific time points

Protocol:

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout ICH E6, *Good Clinical Practice*, the term protocol refers to protocol and protocol amendments.

Racemate:

A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Spare Subject:

A study subject that is included in the drug administration and sample collection regimens of a study but, as per study protocol, whose data will only be included in the PK and statistical analysis if the number of evaluable study subjects drops below a pre-specified number due to subject dropouts and/or withdrawals (use of spare subjects is not acceptable).

Sponsor:

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Swing:

$[(C_{maxSS} - C_{minSS}) / C_{minSS}]$

Tau:

Dosing Interval

T_{max}:

Time to maximum observed concentration

$t_{1/2}$:

Half-life