M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2024
ICH – Multidisciplinary

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FOREWARD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION (1)[2]

A. Objective (1.1)

This guideline is intended to provide recommendations on conducting bioequivalence (BE) studies during both development and post-approval phases for orally administered **immediate-release**[3] (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(ies) when an alternate approach is proposed or taken.

B. Background (1.2)

1. Bioequivalence (1.2.1)

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, for instance, orally administered solutions if BE studies are deemed necessary, and non-orally administered drug products 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

[1] This guidance was developed within the Expert Working Group (Multidisciplinary) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at Step 4 of the ICH process, July 2024. At Step 4 of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] The numbers in parentheses reflect the organizational breakdown of the document endorsed by the ICH Assembly at Step 4 of the ICH process, July 2024.

[3] Words found in the GLOSSARY (p. 19) are bolded at first use in this guidance.

pivotal developmental and 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(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 dosage forms as delineated in ICH M9, *Biopharmaceutics Classification System-Based Biowaivers*.

2. Data Integrity (1.2.2)

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 organizations 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.

C. Scope (1.3)

M13A, the first guideline in the series, 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. 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 but, 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 labeling, *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 labeling.

II. GENERAL PRINCIPLES IN ESTABLISHING BIOEQUIVALENCE (2)

A. Study Design for Pharmacokinetic Endpoint Bioequivalence Studies (2.1)

1. Study Population (2.1.1)

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. To reduce variability not related to differences between drug 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 performance differences between formulations and to allow extrapolation of the results to populations for which the drug product is intended. 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.

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, the inclusion of male and female subjects in the study should be considered.

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 female subjects of reproductive potential should be considered, and female subjects that are pregnant or lactating should not be included. Male contraception (barrier methods or abstinence) is recommended if drugs have any embryo-fetal toxicity and pose transferability issues to female partners of reproductive potential. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or PK reasons.

2. Study Design (2.1.2)

A randomized, single-dose, crossover study design is recommended when comparing test and comparator 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 (see section 2.2.3.3). In general, the highest to-be-marketed strength should be used in a BE study (see section 2.1.6). If the highest strength of a drug product cannot be administered to healthy subjects for safety and/or tolerability reasons, a single-dose study in healthy subjects using a lower strength may be acceptable. Alternatively, 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 $\mathbf{C_{tau}}$ is stable. In general, whether steady-state has been achieved is assessed by comparing at least three pre-dose concentrations for each formulation. The washout of the last dose of the first treatment period may not need to be completed at the time of switching of the treatment. The number of dosage administrations for the subsequent treatment should be sufficient to reach the new steady-state after switching and allow the elimination of the drug from the previous treatment, *e.g.,* 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 need for a prolonged washout period. In this situation, the recommendations in section 2.2.3.4 should be considered.

Alternative study designs are acceptable, if scientifically justified.

3. Sample Size for Bioequivalence Studies (2.1.3)

The number of subjects to be included in the BE study should be based on an appropriate sample size determination 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** (as defined in the Glossary) 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 results of the bioanalysis being known. The number of subjects with evaluable data for primary statistical analysis in a pivotal BE study should not be less than 12 for a crossover design or less than 12 per treatment group for a parallel design.

4. Test and Comparator Products (2.1.4)

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 assayed 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 drug product to-be-marketed and this should be discussed and justified by the applicant.

For pivotal BE studies, oral test products 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. For example, for tablets and capsules, 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 the case of a production batch smaller than 100,000 units, a full production batch is required.

b) Unless otherwise justified (see section 2.2.2.3), 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.

5. Fasting and Fed Study Conditions (2.1.5)

BE studies should be conducted under standardized conditions that minimize variability to better detect potential PK differences between drug products. For orally administered IR solid dosage forms, single-dose BE studies conducted under fasting conditions typically provide greater discrimination between the PK profiles of two drug products than studies conducted under fed conditions. 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 with special characteristics that result in a higher risk of bioinequivalence due to food effects (see "High-risk products" section below), and hence preclude the extrapolation of BE under fasting conditions to fed conditions. In such cases, BE under fed conditions also needs to be demonstrated. Further, some drug products, although not using a complex formulation and/or manufacturing process, have specific characteristics resulting in a formulation that modulates food effect. For these cases, both fasting and fed studies are needed if not otherwise justified. Such a justification may be supported by, *e.g.,* differences in formulations including qualitative and/or quantitative difference(s) in excipients, the BCS classification of the drug substance, *in vitro* testing such as disintegration and dissolution testing in biorelevant media, pilot study(ies), and modeling, such as validated physiologically-based pharmacokinetic (PBPK) modeling and simulation or semi-mechanistic absorption models, that is fit for the purpose.

When BE studies are necessary, the principles as detailed below with regard to fasting and fed study conditions also apply to bridge formulation and/or manufacturing process changes during pre- or post-marketing phases. Relevant scientific justification such as available relative BA and food effect data can be provided to support deviations from these principles.

<u>High-risk products</u>

High-risk products are those where the drug substance characteristics in combination with the complexity of the formulation design or manufacturing process lead to an increased likelihood that *in vivo* performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed conditions. For these drug 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, co-processed drug substances, lipid-based formulations, nanotechnologies, or other specialized technologies, to ensure sufficient solubility of the drug substance and dissolution of the drug substance from the drug product 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 drug product labeling with regard to food intake, if

safety permits.

Considerations for study design

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 drug 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, *e.g.,* high- or non-high-risk.

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

If safety permits, for non-high-risk products, the following is recommended:

- For a drug product that is labeled 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 BE.
- For a drug product that is labeled to be taken only with food due to PK reasons, *i.e.,* enhancing absorption or reducing variability, a single BE study conducted under fed conditions is recommended to demonstrate BE.
- For a drug product that is labeled to be taken only with food due to tolerability reasons, *e.g.,* stomach irritation or other non-PK reasons, a single BE study conducted under either fasting or fed conditions is acceptable to demonstrate BE.

However, for high-risk products, BE studies should be conducted under both fasting and fed conditions, irrespective of the drug product labeling with regard to food intake, if safety permits.

In cases where BE is recommended in both fasting and fed conditions, it is acceptable to conduct either two separate two-way crossover BE studies or one four-way crossover BE study.

Standardization with regard to meals and water

For studies conducted under fasting conditions, subjects should be fasted for at least 8 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 water of the same temperature and volume, in the range of 150 to 250 milliliters (ml). In single-dose studies and on the PK sampling days in multiple-dose studies, no food should be allowed for at least 4 hours post-dose on each day of drug administration. Meals taken during the in-house portion of a study should be standardized 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 BE study conducted under fed conditions, it is recommended that subjects start the meal 30 minutes before administration of the drug product and completely 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 employ 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 900 to 1000 kcal) meal, which should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. It is recognized 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 labeling, 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 are known to 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. Further, since drug absorption can be impacted by GI transit times and regional blood flows, posture and physical activity need to be standardized.

6. Dose or Strength to be Studied (2.1.6)

For an application with multiple strengths, the strength to be used in the BE study depends on the dose proportionality in PK and the solubility of the drug substance. 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, based on maximal concentration (**C_{max}**) and area under the concentration *vs.* time curve (**AUC**), 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 labeled dose range and the total dose is safe for administration to the study subjects.

To determine dose proportionality in PK, the applicant should refer to the approved drug product labeling for the comparator. If such information is lacking, the applicant should consider all available sources of data. Assessment of dose proportionality should generally consider single-dose studies and should consider C_{max} and AUC as appropriate PK parameters for this purpose. In general, PK can be considered dose proportional if the difference in dose-adjusted mean C_{max} and AUC is no more than 25% when comparing the range of strengths proposed. For the purpose of an additional strength waiver, AUC and C_{max} are evaluated to demonstrate proportionality, however, should the available data establish dose proportional PK for AUC but the available data for C_{max} are insufficient, *e.g.,* due to variability, to make a conclusion, the PK can be treated as dose proportional. If data are not available to establish dose proportionality, then BE studies should be conducted with the lowest and highest strengths of the proposed series

of strengths.

For non-proportional increases in AUC and/or C_{max} with increasing dose there may be a difference between strengths in the sensitivity to detect potential differences between formulations.

In cases of documented greater than proportional increases in AUC and/or C_{max} with increasing dose over the range of strengths proposed, the BE study should, in general, be conducted at the highest strength.

In cases of documented less than proportional increases in AUC and/or C_{max} with increasing dose over the range of strengths proposed, BE should be established with the lowest strength if this 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 with both the lowest and highest strengths. If the reason for less than dose proportionality is unknown, BE studies should be conducted with both the lowest and highest strengths. If the drug product is high-risk (see section 2.1.5), in general, a fasting and fed BE study at the highest strength and a fasting BE study at the lowest strength are needed.

7. Moieties to be Measured (2.1.7)

a. Parent vs. Metabolite (2.1.7.1)

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, as 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.

b. Enantiomers vs. Racemates (2.1.7.2)

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
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.

8. Considerations for Sampling Schedule (2.1.8)

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 time to maximum observed concentration ($\mathbf{t_{max}}$) and sufficient samples to ensure a reliable estimate of the extent of exposure, which is achieved when $\mathbf{AUC_{(0\text{-}t)}}$ covers at least 80% of $\mathbf{AUC_{(0\text{-}inf)}}$. The sampling period should generally be at least three times the terminal elimination half-life of the drug, unless a suitable truncated AUC, *i.e.,* $\mathbf{AUC_{(0\text{-}72h)}}$, 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 the apparent terminal elimination rate constant ($\mathbf{k_{el}}$) 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 $\mathbf{AUC_{(0\text{-}tauSS)}}$.

a. First Point C_{max} (2.1.8.1)

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 PK properties of the drug and selection of a suitable early sampling schedule. For example, for drug products with rapid absorption, collection of blood samples at an early time point, between 5 and 15 minutes after dosing, followed by additional sample collections, *e.g.,* two to five samples in the first hour after dosing, is usually sufficient to assess peak drug concentrations. When absorption is rapid, time points earlier than 5 minutes are generally not expected.

For subjects where C_{max} occurs at the first post-dose sampling time, the actual C_{max} may have been missed as it could have occurred at an earlier time point. When this occurs, the robustness of the study results in relation to the potential missed C_{max} should be discussed. This could include additional analysis where data from the affected subjects are removed from the analysis.

b. Long Half-life Drugs and Truncated AUC Considerations (2.1.8.2)

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 drug 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 adequate to ensure completion of GI transit of the drug product and absorption of the drug substance.

c. Early Exposure (2.1.8.3)

For orally administered IR drug products, BE can generally be demonstrated by measurement of rate and extent of absorption, *i.e.,* C_{max} and $AUC_{(0-t)}$. However, in some situations, C_{max} and $AUC_{(0-t)}$ may be insufficient to adequately assess the BE between two drug 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**) or t_{max}, may be applied. In the case of pAUC, it 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.

B. Data Analysis for Non-Replicate Study Design (2.2)

1. Considerations for the Bioequivalence Analysis Population (2.2.1)

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

a. Removal of Data Due to Low Exposure (2.2.1.1)

BE studies typically have 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 drug 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, to the extent 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 one subject in each study, and may bring the reliability of dose administration into question.

Data from redosing studies, *i.e.,* studies where a subgroup of subjects from the original study is dosed again, 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. Presentation of Data (2.2.2)

a. Concentration-Time Data (2.2.2.1)

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.

b. Pharmacokinetic Analysis (2.2.2.2)

For single-dose studies, the following PK parameters should be tabulated for each subject-formulation combination: (1) primary parameters for BE analysis: $AUC_{(0\text{-}t)}$, C_{max}, and, where applicable, early exposure parameters (see section 2.1.8.3), 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 $\mathbf{t_{1/2}}$. 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 number of observations, geometric mean, coefficient of variation, median, arithmetic mean, standard deviation, minimum, and maximum. Each PK parameter should be calculated 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 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: $\mathbf{C_{maxSS}}$ and $AUC_{(0\text{-}tauSS)}$, and (2) additional parameters for analysis: C_{tauSS}, $\mathbf{C_{minSS}}$, $\mathbf{C_{avSS}}$, 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 $t_{1/2}$.

c. Potency Differences in Lots (2.2.2.3)

The results from the potency assay of the test and comparator products should be submitted, and the test product batch and the comparator product batch potencies should not differ by more than 5%. 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.

3. Statistical Analysis (2.2.3)

a. General Considerations (2.2.3.1)

The statistical analyses should include all data for all subjects who provide evaluable data for the drug 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 subjects with evaluable data for primary statistical analysis for a crossover design or for each treatment arm for a parallel design.

In studies with more than two treatment arms, *e.g.,* a four-period study examining fasting and fed conditions (see section 2.1.5) or a three-period study including two comparator products or two test products (see section 2.2.5), the analysis for each comparison should be conducted excluding the data from the treatment arms that are not relevant for the comparison in question.

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 PK data should be transformed prior to analysis using a logarithmic transformation.

The model to be used for the statistical 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. *Post hoc* and data-driven adjustments are not acceptable for the primary statistical analysis.

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 randomization scheme should be provided.

b. Crossover Design Studies (2.2.3.2)

Randomized, non-replicate, crossover design studies should be analyzed using an appropriate parametric method, *e.g.,* general linear model or mixed model. 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. The primary statistical analyses should include all data for all

subjects who provide evaluable data for both the test and comparator products.

c. Carryover (2.2.3.3)

A test for carryover is not considered relevant and no decisions regarding the analysis, *e.g.,* analysis of the first period only, should be made based on such a test. In crossover studies, the potential for carryover 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.

In single-dose studies, 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 primary statistical analysis should be performed excluding the data from that period, which may result in the exclusion of the subject as discussed in section 2.2.3.2.

d. Parallel Design Studies (2.2.3.4)

The statistical analysis for randomized, 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 randomization procedure based on a limited number of known relevant factors is therefore recommended. Those factors are also recommended to be accounted for in the primary statistical analysis.

e. Multi-Group Design Studies (2.2.3.5)

Sample size requirements and/or study logistics may necessitate studies to be conducted with groups of subjects. The BE study should be designed to minimize 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. The statistical model should take into account the multi-group nature of the BE study, *e.g.,* by using a model including terms for group, sequence, sequence x group, subject within sequence x group, period within group and formulation. The group x treatment interaction term should not be included in the model. However, applicants should evaluate potential for heterogeneity of treatment effect across groups and discuss its potential impact on the study data, *e.g.,* by investigation of group x treatment interaction in a supportive analysis and calculation of descriptive statistics by group.

In multi-center 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 in the study protocol and a sensitivity analysis is recommended.

4. Bioequivalence Criteria (2.2.4)

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 $AUC_{(0-t)}$ (see section 2.1.8.2).

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 (see section 2.1.8.3).

5. Multiple Comparator and Multiple Test Product Studies (2.2.5)

a. Multiple Comparator Products (2.2.5.1)

It may be necessary to demonstrate BE between a test product and multiple comparator products to meet requirements from multiple jurisdictions. 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.

In studies with multiple comparator products, 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 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 a 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.

b. Multiple Test Products (2.2.5.2)

It may be necessary to demonstrate BE between multiple test products and the comparator product, *e.g.,* to include different test formulations that may need to be investigated 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 *vs.* the comparator product, no alpha adjustment is needed.
b) If the objective is to show BE for any of the test formulations, multiplicity (alpha) adjustment may be needed.

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

III. SPECIFIC TOPICS (3)

A. Endogenous Compounds (3.1)

In some cases, **endogenous compounds** are identical to the drug that is being administered. For

these drugs, 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 standardizing 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 carryover effects cannot be readily detected. If a baseline correction results in a negative concentration value, the value should be set 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.

When considered necessary to ensure adequate separation of treatment-induced concentrations over baseline, a high dose may be administered in BE studies of endogenous compounds if the dose is well tolerated and dose proportionality in PK is maintained. Alternatively, the need for baseline correction may be avoided by enrolling study subjects with low or no production of the endogenous compounds.

B. Other Immediate Release Dosage Forms (3.2)

1. Orally Disintegrating Tablets (3.2.1)

Orally disintegrating tablets (ODTs) should be administered in BE studies according to the comparator product labeling with regard to intake of water.

If the comparator product labeling 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 labeling and compared with the comparator product administered as per its labeling.

If the new intended label use/instructions state that the ODT can be taken with and without

water, a 3-arm BE study is recommended to demonstrate BE of the ODT administered with and without water compared to the comparator product administered as per its labeling.

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.

2. Chewable Tablets (3.2.2)

Chewable tablets should be administered in BE studies according to the comparator product labeling 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 labeling and compared with the comparator product administered as per its labeling.

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

3. Oral Suspensions (3.2.3)

For tablets, granules, and powders labeled 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 labeling.

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

C. Fixed-Dose Combination (3.3)

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.

BE of all components (drugs) in the fixed-dose combination product can be demonstrated with a single study, or a separate study for each component, if justified.

D. pH-Dependency (3.4)

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-modifying 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. Therefore, in certain situations, an additional BE assessment with concomitant treatment of a pH-modifying drug product would generally be necessary if all of the following criteria are met:

a) The drug products under comparison contain a drug substance with pH-dependent solubility in the pH range of 1.2 - 6.8.
b) The drug product is expected to be taken with acid reducing agents, *e.g.,* proton pump inhibitors, or is going to be used in certain populations, *e.g.,* patients with achlorhydria.
c) There are qualitative or quantitative differences in the pH-modifying excipient(s), significant differences in manufacturing process that may affect drug absorption due to gastric pH differences, or differences in the salt or polymorphic form that possess a different pH-dependent solubility.

For non-high-risk products, the study with concomitant treatment of a pH-modifying drug product should be conducted under the same condition with regard to fasting or fed conditions as stipulated in section 2.1.5.

If the drug product is high-risk (see section 2.1.5), in general a fasting BE study with concomitant treatment of pH-modifying drug product would be necessary in addition to fasting and fed BE studies. However, for drug products labeled to be taken only with food, the study with concomitant treatment of a pH-modifying drug product should be conducted under fed conditions.

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. Modeling and simulation, *e.g.,* appropriately validated PBPK modeling or semi-mechanistic absorption models, and virtual BE simulation, may be used to further assess the risk of bioinequivalence.

IV. DOCUMENTATION (4)

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 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 dosage form, **batch number**, marketing authorization holder, expiration date, and country of purchase should be stated.

Certificates of analysis (CoA(s)), or equivalent documents, of test and comparator batches used in the study should be included in an appendix to the study report. It is recommended that the CoA(s) be generated within 6 months prior to the start of period 1 of the study.

The identity of the drug products used in the study should be provided, *i.e.*, pharmaceutical dosage form, strength, batch number, and measured content (% of label claim). The batch size, manufacturing date and, if available, the expiration 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, 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 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 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 randomization 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.

GLOSSARY (5)

Applicant:

The entity submitting the application for marketing authorization 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 observed 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 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.

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 that 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:

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

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.

k_{el}:

The apparent terminal elimination rate constant

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 organization of a study. The protocol usually also gives the background and rationale for the study, 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 analyses if the number of subjects with evaluable data for primary statistical analysis 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 organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Swing:

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

Tau:

Dosing Interval

t_{max}:

Time to maximum observed concentration

$t_{1/2}$:

The apparent terminal elimination half-life