M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms Questions and Answers

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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FOREWORD

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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M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms Questions and Answers 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.

(PREFACE)

In response to questions posted to the International Council for Harmonisation (ICH) draft guidance for industry *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms* comment period, several questions and answers have been developed to provide clarity around some of the concepts related to bioequivalence study design and data analysis covered in the guidance.

This question and answer (Q&A) document is intended to provide additional clarification and improve harmonization of bioequivalence study design and data analysis.

The scope and organization of this Q&A document follow that of the ICH guidance for industry *M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms* (October 2024) (ICH M13A).[2]

[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] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Contains Nonbinding Recommendations

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

I. INTRODUCTION (1)[3]

Table 1: Q&A for Section I (1) of ICH M13A

Number	Date of Approval	Question	Answer
		None	

[3] 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.

II. GENERAL PRINCIPLES IN ESTABLISHING BIOEQUIVALENCE (2)

Table 2: Q&A for Section II (2) of ICH M13A

Number	Date of Approval	Question	Answer
2.1	**July 2024**	Why are a minimum of 12 subjects required for a pivotal bioequivalence (BE) study?	The requirement for a minimum of 12 evaluable subjects in pivotal BE studies for a crossover design, or a minimum of 12 per treatment group for a parallel design, is an established practice by regulatory agencies. The appropriate number of subjects for a BE study can be estimated based on knowledge of the formulation performance *in vivo* and the drug's PK variability, *e.g.*, from pilot relative bioavailability studies. In general, the BE study should be designed with sufficient subjects to have *a priori* power of at least 80% to show equivalence for the BE parameters within a prespecified acceptance range, *i.e.*, 0.80 - 1.25. It should be noted *a posteriori* power is not relevant.
2.2	**July 2024**	What is the minimum production batch size for dosage forms other than tablet or capsule formulations?	In principle, as for tablets and capsules, the production batch size for other types of formulations should correspond to at least 10% of the production scale batch, but other batch sizes may be considered based on manufacturing considerations. The applicants should align with regional Quality guidelines.

Number	Date of Approval	Question	Answer
2.3	**July 2024**	For a non-high-risk product that is labeled to be taken only with food due to tolerability reasons, *e.g.*, stomach irritation, and not due to PK reasons, why is it acceptable to conduct a single BE study under either fasting or fed conditions?	When a product is labeled to be taken with food for tolerability reasons, it is often because tolerability issues occur with repeated or chronic administration of the product, or it is to avoid minor GI irritation that might result from a single administration of the drug product. For these non-high-risk products, the state of administration (fasting or fed) is not expected to influence the PK comparability of the products. Thus, no impact on the BE outcome is anticipated. As noted in section 2.1.5 of M13A, BE studies conducted under fasting conditions typically provide better discrimination of the PK profiles of two drug products. Therefore, if the study sponsor and the relevant ethics committee agree that administration of the drug products under fasting conditions is feasible, then such a study can be employed because of its discriminative advantages. However, should it be decided that the tolerability is such that a study conducted under fasting conditions may pose a safety risk for the study subjects, a study under fed conditions can be conducted.
2.4	**July 2024**	Why are studies conducted under fasting and fed conditions recommended for high-risk products?	Formulation and/or manufacturing characteristics of orally administered IR drug products containing high solubility drug substance(s) usually have a limited impact on the dissolution and absorption of the drug substance(s) assuming relatively rapid dissolution is observed. In contrast, drug products containing low solubility drug substance(s) are often developed to enhance the dissolution and bioavailability, or to modify food and/or gastric pH effects, which might otherwise be limited by solubility factors. Such drug products with specific formulation and/or manufacturing technology to enhance PK performance are considered high-risk products because of the potential interaction between the performance enhancing characteristic(s) of the drug product and GI tract conditions. For these drug products, there is an increased risk that changes in

Number	Date of Approval	Question	Answer
2.4 (cont'd)	**July 2024**		GI conditions could alter the PK performance of two products for which there are differences in the performance enhancing characteristic(s), whether the differences are related to the formulation or manufacturing technologies employed. Differences in the process, *e.g.*, hot melt extrusion or spray drying, or excipients, *e.g.*, pH-independent polymers, hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP), or a pH-dependent polymer, hypromellose acetate succinate (HPMCAS) used to produce a solid dispersion could result in a differential interaction with GI conditions. Such a difference might not be observed if the products are compared under either fasting or fed conditions alone. It is important to assess the sensitivity of these products to different GI conditions because, in clinical practice, there is often wide variability in GI conditions that is not adequately addressed by BE assessment under either fasting or fed conditions alone.

Number	Date of Approval	Question	Answer
2.5	**July 2024**	For high-risk products, why is it necessary to conduct BE studies under both fasting and fed conditions even if the comparator product labeling recommends administration under only one condition, *i.e.*, either only under fasting or only under fed conditions?	As discussed above, PK performance of low solubility drug substances enhanced via complex formulation and/or manufacturing technologies may be sensitive to varying GI conditions such that differences in these enhancing characteristics between drug products could result in different performance under certain GI conditions. As there is substantial variability in GI conditions following different meals and there can be significant variability in the degree to which patients are truly in the fasting state when drug products are administered, it is not possible to assess the potential differences in performance of a high-risk product under fasting or fed conditions alone. The risk of bioinequivalence between high-risk products is best minimized by assessing the relative performance of the test and comparator products over a range of GI conditions.

Number	Date of Approval	Question	Answer
2.6	**July 2024**	Why is it acceptable to employ either a low-fat, low-calorie meal or a high-fat, high-calorie meal when only one BE study conducted under fed conditions is recommended for a non-high-risk product?	For non-high-risk products, the state of administration (fasting or fed) is not expected to influence the PK comparability of the products. A high-fat, high-calorie meal is designed to provide the greatest perturbation in GI physiology compared to fasting conditions. Therefore, for a high-risk product, BE studies conducted under both fasting and high-fat, high-calorie fed conditions are recommended to assess performance at the extremes of the spectrum of GI physiological conditions. For non-high-risk products where only a single BE study is recommended, a BE study conducted under fasting conditions is generally preferred because it typically provides the greatest discrimination between the PK profiles of the test and comparator products. However, in cases where a single study conducted under fed conditions is recommended for a non-high- risk product, a more moderate meal, which still addresses the 'with food' recommendation, would have a less severe impact on GI conditions and better reflect the type of meals a patient is likely to consume, could be more suitable for such BE studies. The use of a low-fat, low-calorie meal reduces GI perturbation compared to a high-fat, high-calorie meal, while still addressing the need for food. M13A does not preclude the use of a high-fat, high-calorie meal for BE studies with non-high-risk products. It is recognized that a single meal cannot represent the diverse range of meals patients may consume prior to drug product intake. Therefore, a meal more consistent with the typical caloric and fat content consumed by patients may be an optimal approach for a single BE study under fed conditions.

Number	Date of Approval	Question	Answer
2.7	**July 2024**	What is meant by drug products that are not considered to have complex formulation or a complex manufacturing process, but still have special characteristics designed to modulate a food effect?	Sometimes an unwanted food effect is observed during drug product development. In these cases, formulations may be modified to prevent such a food effect. As an example, a significant food effect for an initial formulation of a low solubility drug was observed during development. Due to the proposed indicated use, administering the drug product under fasting conditions only was not considered desirable. By changing the manufacturing process, *e.g.*, micronizing the drug substance and adding a surfactant, the food effect was avoided thereby enabling drug product administration independent of food. This final formulation would not be considered a complex formulation *per se.* However, if a test product is not based on the same formulation and/or manufacturing processes, a food effect cannot be excluded even though the drug products are not considered to have complex formulations. Therefore, a BE study under fasting conditions alone is considered insufficient. It is recognized that these situations are difficult to identify. However, applicants should be aware that using manufacturing processes different from the comparator product may result in different formulation performance compared to the comparator product.

Number	Date of Approval	Question	Answer
2.8	**July 2024**	Should the highest strength be administered to patients, or can a lower strength be given to healthy subjects instead if 1) there is less than proportional PK across the product strengths due to solubility or for unknown reasons and 2) the highest strength cannot be administered to healthy subjects due to safety reasons?	If there is less than dose proportional PK due to solubility or unknown reasons, BE studies should be conducted at both the highest and lowest strengths. Thus, if the highest strength cannot be administered to healthy subjects due to safety reasons, the study with the highest strength should be conducted in patients. Using a lower strength (an intermediate strength) instead in healthy subjects is not recommended in this instance because the type of nonproportionality necessitates that BE should be investigated at a dose in the non-proportional portion of the dose range. The study of the lowest strength can be conducted in healthy subjects provided that its use in such subjects has acceptable safety.
2.9	**July 2024**	When is it appropriate to remove data from statistical analysis for BE assessment?	M13A stipulates that data should be removed from the statistical analysis because of high pre-dose concentrations (see section 2.2.3.3) and may be removed because of low exposure in exceptional cases (see section 2.2.1.1). In addition to the reasons specifically stated above, study protocol deviations may necessitate removal of data from the statistical analysis. The following are a few examples that may support such removal: 1. A subject does not complete the pre-dose meal in a fed study. 2. A subject completes a study period but is deemed to have insufficient number of samples to allow for an accurate estimation of the primary PK parameters. 3. A subject experiences emesis within two times the expected median t_{max}. 4. In rare cases, a subject experiences an adverse event that may change GI motility during the study period that may

Number	Date of Approval	Question	Answer
2.9 (cont'd)	**July 2024**		affect drug absorption, *e.g.*, diarrhea within two times the expected median t_{max}. 5. A subject who does not complete the study due to AEs, non-compliance or withdrawal of consent due to personal reasons. The specific reasons for protocol violation that may lead to subject removal from statistical analysis should be pre-specified in the protocol. Exclusion of data from the statistical analysis for any reason other than those specifically stated in section 2.2 of M13A, should be documented prior to bioanalysis. In a 2-way crossover design, if data from one period are excluded, the subject should not be included in the statistical analysis. In more complex study designs, removal of subject data from only one period may not result in the complete removal of the subject from the statistical analysis.

Number	Date of Approval	Question	Answer
2.10	**July 2024**	M13A recommends that group-by-treatment interactions should be evaluated. How can these interactions be limited?	Subjects can be considered as a group if, for example, they participate in a study as a cohort at one study site over a particular time span. In a multi-site study, even with balanced treatment/sequence-blocking, group differences are likely unavoidable. In a single-site study, dosing subjects in groups may be unavoidable for logistic reasons. The following measures should be considered to minimize group effects: 1. Start dosing all groups at the same clinic over a specific time span, *e.g.*, within a few weeks. 2. Follow the same protocol requirements and procedures for all groups, and recruit subjects from the same enrollment pool thereby achieving similar demographics among groups. 3. Randomly assign subjects to group and treatment arm (or treatment sequence) at the study outset. Assign an equal sample size to each group when feasible, *e.g.*, when healthy subjects are enrolled.
2.11	**July 2024**	If multiple test products are administered in a BE study, when is multiplicity correction recommended?	If there are multiple test products included in a BE study, the study objectives must be clearly stated. An appropriate strategy to account for multiplicity should be provided in accordance with the objectives. This may warrant multiplicity correction. If the objective of the BE study is to demonstrate BE for at least one pair-wise comparison, and not necessarily all the multiple test products, *e.g.*, test product 1 *vs.* comparator product or test product 2 *vs.* comparator product, the inflated

Number	Date of Approval	Question	Answer
2.11 (cont'd)	**July 2024**		type I error and increased chance of a false positive result has to be acknowledged, and multiplicity correction (alpha adjustment) needs to be considered. Applicants are advised to consult their regulatory agency. The choice of alpha adjustment method should be justified *a priori* by the sponsor. Although conservative, Bonferroni correction is one possibility. Other suitable alpha adjustment methods can be considered. Hierarchical testing can also be used, where each test product is assessed *vs*. the comparator product in a pre-specified order. If there is a test product for which BE with the comparator product is not demonstrated, then BE of that test product and of all those later in the hierarchy cannot be concluded. Formally, there is no need for multiplicity correction for each individual test, but the type I error (consumer risk) is still controlled. Most likely, the pair-wise comparison would start with the test product for which the highest likelihood of a positive BE outcome is assumed. Otherwise, the risk of failing the entire BE analysis after the first pair-wise comparison is high. As an example, a comparator product is an ODT labeled to be administered with water. The hierarchy is to first assess BE of the test product and the comparator product both administered according to the comparator product labeling, *i.e.*, with water, then assess BE of the test product administered without water with the comparator product administered according to its labeling, *i.e.*, with water. If the first comparison fails, the study is considered failed and BE for all test products is rejected. If the first comparison passes, then the pair-wise comparisons can continue.

Number	Date of Approval	Question	Answer
2.11 (cont'd)	**July 2024**		Test product formulations may be developed for specific regions. As an example, formulation development includes the use of a certain excipient under patent, which applies to some regions and not others. Two formulations are developed, one with the certain excipient, intended for the region(s) not covered by the patent, and the other without the certain excipient, intended for the region(s) covered by the patent. As such, the BE study is conducted with both region-specific test products and one comparator product acceptable in all regions. In this case, an alpha adjustment to appropriately control the type I error (consumer risk) is not needed. Patients in the region with the successful test products are not affected by the failed test product(s) for the other region(s). If a BE study can only be considered positive if all test products or intended label use/instructions are demonstrated to be BE to the comparator product, no alpha adjustment is needed. However, in this case controlling type II error should be considered and the study should be powered sufficiently to demonstrate BE for all test products or methods of administration. As an example, for a new ODT developed as a line extension to another orally administered IR drug product, *e.g.*, a tablet, BE studies may be conducted to determine whether the ODT is BE to that existing tablet product. If the new intended label use/instructions are intended to 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.

III. SPECIFIC TOPICS (3)

Table 3: Q&A for Section III (3) of ICH M13A

Number	Date of Approval	Question	Answer
3.1	**July 2024**	In the context of BE studies, why is it recommended that if a baseline correction results in a negative concentration value, the value should be set equal to zero, especially considering that software can handle negative values when calculating AUCs?	Physiological implausibility and analytical variability of negative drug concentrations are the rationale for setting negative concentration values to zero after baseline correction. In PK, negative concentrations do not have a meaningful biological interpretation and may simply be due to insufficient separation between endogenous concentrations and treatment-induced concentrations.
3.2	**July 2024**	Given that M13A offers the opportunity to enroll subjects with low or no production of endogenous compounds and considering that baseline correction usually increases the variability of the PK parameters, is there a defined threshold where no baseline correction is required in BE studies?	There is no defined threshold above which a baseline correction is required. If there are no quantifiable concentrations of the endogenous compound, no baseline correction is needed. The purpose of baseline correction is to accurately assess BE between two drug products without causing additional complexity. The decision to apply baseline correction in BE studies should be based on a balance between methodological accuracy and the practical aspects of study design. While baseline correction may increase the variability of the PK parameters, this may not be the case for all endogenous compounds.
3.3	**July2024**	Does M13A apply to BE studies for oral suspensions?	Although suspension is not a dosage form covered under M13A, which focuses on oral solid dosage forms, the same principles in M13A for oral solid dosage forms can be used for an oral suspension to establish BE.

Number	Date of Approval	Question	Answer
3.4	**July 2024**	What dose should be administered in a BE study where both test and comparator products are oral suspensions?	If only one strength (concentration) of an oral suspension exists, *e.g.*, 10 milligram (mg)/milliliter (ml), and the oral suspension is the only dosage form, the dose to be employed in the BE study should follow the recommended dosing, or one of the doses, as mentioned in the labeling, taking into consideration that the dose administered is safe and should result in sufficiently high plasma concentrations considering the bioanalytical sensitivity. If only one strength (concentration) of the oral suspension exists, *e.g.*, 10 mg/ml, but in addition, for instance, a capsule or tablet formulation is marketed for the same indication, the dose to be administered in the BE study comparing the test and comparator oral suspension should adhere to section 2.1.6 of M13A. For example, an oral suspension of 10 mg/ml was developed for patients with difficulties swallowing, and 50 mg and 100 mg capsule strengths are also marketed for the same indication. As such, the labeling includes the 10 mg/ml oral suspension, the

Number	Date of Approval	Question	Answer
3.4 (cont'd)	**July 2024**		50 mg capsule, and the 100 mg capsule, and the oral suspension and capsules can be used interchangeably. The following three scenarios may occur: 1. As per section 2.1.6 of M13A, the highest strength should be administered in the case of a proportional or a greater than proportional increase in AUC and/or C_{max} with increasing dose. For the capsule formulation, the 100 mg capsule strength should be administered in the BE study. Consequently, a 100 mg dose, *i.e.*, 10 ml of the oral suspension should be administered in the BE study. 2. As per section 2.1.6 of M13A, the lowest strength should be administered in the case of a less than proportional increase in AUC and/or C_{max} with increasing dose if the nonproportionality is due to saturation of absorption. For the capsule formulation, the 50 mg capsule strength should be administered in the BE study. Consequently, a 50 mg dose, *i.e.*, 5 ml of the oral suspension should be administered in the BE study. 3. As per section 2.1.6 of M13A, the lowest and the highest strength should be investigated in the case of a less than proportional increase in AUC and/or C_{max} with increasing dose if the nonproportionality is due to limited drug solubility or if the reason is unknown. For the capsule formulation, the 50 mg and 100 mg capsule strengths should each be administered in a BE study. Consequently, 50 mg and 100 mg doses, *i.e.*, 5 ml and 10 ml of the oral suspension should each be investigated in BE studies.

Number	Date of Approval	Question	Answer
3.5	**July 2024**	What strength and dose should be administered in a BE study where both test and comparator products are oral suspensions, and more than one strength of the oral suspension exists?	The dose to be administered in the BE study should adhere to section 2.1.6 of M13A and should also consider whether the oral suspensions are the only dosage form (see Question 3.4). In the case of dose proportional PK and multiple strengths (concentrations) of an oral suspension, *e.g.*, 5 mg/ml and 10 mg/ml, it is acceptable to administer the highest strength in the BE study. In the case of non-proportional PK, refer to the scenarios in the Answer to Question 3.4 to determine the appropriate strength(s) to be studied. A biowaiver for additional strengths, *e.g.*, 5 mg/ml, may be requested, if the criteria for a biowaiver of additional strengths are fulfilled.

Number	Date of Approval	Question	Answer
3.6	**July 2024**	Can you provide an example of a clinical study design for an additional BE study with concomitant treatment of a pH-modifying drug product, and for the types of drug substance or drug product that can be affected?	Subjects should be pre-treated with a proton pump inhibitor (PPI) for several days, *e.g.*, 4 to 5 days to reach pharmacodynamic steady-state before administering the test or comparator products. The elevating effect of a PPI on gastric pH, *e.g.*, mean pH over 24 hours, percentage of the time when the pH ≥4.0 in a 24-hour interval, is dependent on the individual PPI and its dose. The selected PPI should have minimal effect on the PK of the drug via other interacting mechanisms and the dose of the PPI should provide a near maximum effect on gastric acid suppression, *i.e.*, pH elevation. If no suitable PPI can be dosed, alternative acid-reducing agents may be considered with suitable justification for their selection. Examples of drug products where elevated gastric pH may affect BE outcomes include palbociclib[1,2] and different salt forms of prasugrel[3,4]. References: 1. Draft Guidance on Palbociclib USFDA PSG_212436 2. Palbociclib hard capsule 75 mg, 100 mg and 125 mg and film-coated tablet 75 mg, 100 mg and 125 mg product-specific bioequivalence guidance. EMA/CHMP/802679/2018 Rev.1* Corr. 1** 3. Prasugrel hydrochloride film-coated tablets 5 mg and 10 mg product- specific bioequivalence guidance. EMA/CHMP/158772/2016/Rev.1. 4. Seiler, D., Doser, K. & Salem, I. Relative bioavailability of prasugrel free base in comparison to prasugrel hydrochloride in the presence and in the absence of a proton pump inhibitor. Arzneimittelforschung 61, 247–251 (2011).

Number	Date of Approval	Question	Answer
3.7	**July 2024**	Why are fed BE and clinical PPI drug-drug interaction (DDI) studies not considered adequate or acceptable to address the risk of bioinequivalence at elevated gastric pH?	This risk is not addressed by fasting and fed BE studies, as the multiple ongoing processes in the fed state, *e.g.*, increase in volume of gastric contents, delayed gastric emptying, increased bile salt concentrations in the small intestine, could underestimate the impact of a sustained increase in gastric pH on drug dissolution and absorption. While the effect due to an acid reducing agent (ARA) may be modulated when the drug is given in the fed state, the fed BE study would not make the study with a PPI unnecessary. For a drug with pH susceptibility and labeled to be given with food, a PPI study under fed conditions could still be requested. Clinical DDI studies in the presence of ARAs address the question of whether the comparator product performs differently under conditions of elevated gastric pH. However, they do not provide definitive information on the likelihood of a difference in performance between test and comparator formulation at elevated gastric pH. The absence of an ARA effect on the comparator product may be due to deliberate formulation design to overcome such an effect, and these features may not be reproduced in the test product. Therefore, it cannot be assumed that the test and comparator product would be BE at elevated gastric pH. ARA interaction data may, however, form part of the risk assessment, when assessed with information on formulation design and dissolution properties.

IV. DOCUMENTATION (4)

Table 4: Q&A for Section IV (4) of ICH M13A

Number	Date of Approval	Question	Answer
4.1	**July 2024**	If the relevant BE studies conducted with the same formulation under the same study conditions result in different BE outcomes, what action should be taken?	M13A recommends that all relevant BE studies conducted, regardless of the study outcome, should be provided. If, for a particular formulation at a particular strength, multiple pivotal studies result in inconsistent BE conclusions, the totality of the evidence should be considered. The applicant should discuss the results and justify the BE claim. When relevant, a combined analysis of all studies may be considered as a sensitivity analysis in addition to the individual study analyses. It is not acceptable, however, to pool studies which fail to demonstrate BE without a study that passes. If there are differences in the study conditions, *e.g.*, sampling times, fasting or fed conditions, or method of administration, pooling is not justifiable. A different number of subjects is not considered a difference in study conditions.