CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

REGULATORY GUIDELINES FOR CONDUCTING BIOAVAILABILITY AS PER USFDA

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Abstract:
Bioavailability studies are critical studies used to support INDs and NDAs. BA refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. This data is used to determine the fraction of drug absorbed and a drugs pharmacokinetics. FDA's guidance focuses on the use of pharmacokinetic studies to document bioavailability data. Specifically, FDA provides recommendations on type of study, population composition, dosing, analytical methods, measures of systemic exposure, and other approaches to support bioavailability. To deliver many drugs to their site(s) of action, we rely on the systemic blood circulation, as opposed to locally acting drug products, such as ointments intended to treat a skin condition. For drug products intended for systemic absorption, bioavailability of a drug from its dosage form is generally determined by comparing its pharmacokinetic profile in blood with that after intravascular administration of the same drug in solution. The present study was aimed to study the need for bioavailability studies, ethical guidelines, experimental designs, pharmacokinetic endpoints, and their statistical evaluations. Specifically, the guidance addresses study design considerations, including in-vivo *and* in-vitro *studies, and assessing BA for various dosage forms. Appendices provide recommendations for approaches for general study design and data handling, guidelines for conducting fed or fasted studies, and guidelines for conducting an* in-vitro *alcohol dose-dumping study.*

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Please cite this article in press CH. Pallavi et al, ***Regulatory Guidelines For Conducting Bioavailability As Per USFDA".,*** *Indo Am. J. P. Sci, 2023; 10(01).*

INTRODUCTION:

This guidance provides recommendations to sponsors and applicants submitting bioavailability (BA) information for drug products in investigational new drug applications (INDs), new drug applications (NDAs), and NDA supplements. This guidance contains recommendations on how to meet the BA requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration. These dosage forms include tablets, capsules, solutions, suspensions, conventional (e.g., immediate-release (IR) drug products) and modified-release (MR) (e.g., extended-release (ER), delayed-release (DR)) drug products. The guidance is also applicable to non-orally administered drug products when it is appropriate to rely on systemic exposure measures to determine the BA of a drug (e.g., transdermal delivery systems and certain vaginal, rectal, and nasal drug products). The guidance provides recommendations on conducting BA studies during the investigational period for a drug intended to be submitted for approval in an NDA and bioequivalence (BE) studies during the postapproval period for certain changes to drug products with an approved NDA.

In August 2021, the FDA issued a separate draft guidance on this topic entitled Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. Furthermore, this guidance does not provide recommendations on studies conducted in support of demonstrating comparability or biosimilarity for biological products licensed under section 351 of the Public Health Service Act (see the FDA guidances entitled Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016) and Considerations in Demonstrating Interchangeability With a Reference Product (May 2019) for more information).

This guidance finalizes the FDA guidance entitled Bioavailability Studies Submitted in NDAs or INDs – General Considerations (February 2019). The February 2019 draft of this guidance revised and replaced the draft guidance. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (March 2014). The FDA considered comments received on the March 2014 guidance when issuing the February 2019 draft of this guidance. The FDA recognizes that this guidance cannot address every issue pertaining to the assessment of BA studies for INDs and NDAs.

BACKGROUND

BA is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

General BA Considerations

BA studies comparing two formulations or two test conditions are usually conducted using a crossover design. For a drug with a long half-life, a parallel design could be more scientifically appropriate.

Pre-approval Changes

The relative BA of formulations used in drug development should compare:

(1) the early and late clinical trial formulations;
(2) the formulations used in clinical trials and stability studies, if different;
(3) the clinical trial formulations and to-be-marketed drug products, if different;
(4) the equivalence of product strengths; and
(5) the comparison of two different products in support of an NDA described in section 505(b)(2) of the FD&C Act. For purposes of this guidance, in each comparison, the new formulation, the formulation produced by a new method of manufacture, or the new strength is the test product, and the prior formulation, the product made using the prior method of manufacture, or the product with the prior strength is the reference product.

Postapproval Changes

• SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)

• SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997)

STUDY DESIGN CONSIDERATIONS

A. In Vivo Studies

1. General Consideration

BA frequently relies on PK measures such as the AUC to reflect the extent of systemic absorption and the Cmax and Tmax to reflect the rate of systemic absorption. PK-based comparisons to describe relative BA assume that measuring the active moiety at the site of action is not possible and that some relationship exists between the concentration of the active moiety in the systemic circulation and the safety and efficacy of the drug. A typical PK study to determine comparative BA is conducted as a crossover study. The crossover design reduces variability in PK measures that are caused by subject-specific factors, thereby increasing the ability to

discern differences in PK measures that are caused by different formulations.

2. Pilot Study

If the sponsor chooses, a pilot trial with a small number of subjects can be carried out before proceeding with a full-scale BA study. The results of a pilot study can:

• Assess the variability in PK measures

• Determine the sample size that achieves adequate power to conduct BA analysis in the full-scale study

• Optimize the time intervals for sample collection

• Determine the length of the washout period needed between treatments.

3. Full-Scale Study

General recommendations for a standard BA or BE study based on PK measurements are provided in appendix A. Non-replicate, crossover study designs are recommended for BA studies of IR and MR dosage forms.

4. Study Population

In general, BA studies should be conducted in healthy subjects 18 years of age or older who are capable of giving informed consent. When safety considerations preclude the use of healthy subjects, it might be preferable and more appropriate to evaluate the BA of a drug in individuals with the disease or condition being studied.

B. Other Approaches To Determine the BA of a Drug

In certain circumstances, other approaches are recommended to determine the BA of a drug. Below are some general considerations regarding these other approaches.

1. In Vitro Studies
2. In Vitro Tests Predictive of Human In Vivo BA
3. PD Studies
4. Comparative Clinical Studies

ASSESSING BA AND DEMONSTRATING BE FOR VARIOUS DOSAGE FORMS

A.Solutions and Other Solubilized Dosage Forms

For oral solutions, elixirs, syrups, tinctures, or other solubilized dosage forms, in vivo BA is generally self-evident, and a requirement of in vivo BA data for a product can be waived based on other data in the application. Even when a comparative study is not needed, characterization of the pharmacokinetics of the drug is required.

B. IR Drug Products

Pre-approval: BA Studies

Postapproval Changes

C. MR Drug Products

MR products include ER (e.g., controlled-release, sustained-release) and DR products.

Pre-approval: BA Studies

Regulations address the purpose and requirements of a BA study for an ER product and stipulate that "the reference material(s) for such a BA study shall be chosen to permit an appropriate scientific evaluation of the ER claims made for the drug product." Appropriate reference products must be one of the following or any combination thereof:

• A solution or suspension of the active drug ingredient or therapeutic moiety

• A currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to approved labeling of the noncontrolled-release drug product

• A currently marketed ER drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the currently marketed ER product

• A reference material other than one described above that is appropriate for valid scientific reasons

Consider in the following example, that a 150-milligram (mg) ER product administered once daily (QD) is being developed given an approved 50-mg IR reference product administered three times a day (TID) or a 75-mg product administered two times a day (BID). For relative BA purposes, the 150-mg ER product administered as a single dose could be compared to either the 50-mg IR reference product administered TID or the 75- mg IR reference product administered BID.

• If multiple ER strengths are being developed, and the ER strengths are not proportionally similar in composition, a single-dose fasted dosage strength equivalence assessment study or a dosage strength proportionality study for the ER product should be conducted. Examples of each are: o If three strengths, 10, 25, and 50 mg, are being developed for a new ER dosage form, the dosage strength equivalence study should be conducted using 5×10 mg strength, 2×25 mg, and 1×50 mg to achieve constancy of dose. o If three strengths, 10, 25, and 50 mg, are being developed for a new ER dosage form, the dosage strength proportionality study should be conducted using 1×10 mg, 1×25 mg, and 1×50 mg.

• A steady-state study should be conducted on the highest strength of the ER product compared to an approved IR reference product and dosed to achieve the equivalent total dose of the ER product.

New ER product (ERnew) comparison to an approved ER product (ER_{old}) with a different dosing interval (i.e., where ERnew and ERold have unequal dosing intervals)

• The recommendations for the development of a new ER product given an approved ER product with a different dosing interval are the same as outlined in the previous section C.1.a. (i.e., development of a new ER formulation given an already approved IR product) except for the choice of the reference product. In this case, the reference product could be either the approved ERold or the IR product.

c. New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with the same dosing interval.

• A single-dose, high-fat, food-effect study should be conducted using the highest ERnew strength.

Postapproval Changes

An FDA guidance entitled SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997) provides recommendations on the types of in vitro dissolution and in vivo BE studies for MR drug products, including ER drug products, to support specific postapproval changes. For postapproval changes, the FDA recommends that the sponsor conduct in vitro or in vivo comparisons between the product made before the change and the product made after the change.

ADDITIONAL INFORMATION ON IN VITRO APPROACHES

A. General Considerations

The regulations indicate that if in vivo BA or BE data are required for a product, a sponsor can seek a waiver of these requirements under certain circumstances. For example, sometimes in vivo BA or BE is self-evident based on certain characteristics of the drug product, and no additional in vivo data are required. In other circumstances, a requirement for in vivo BA or BE data can be waived, and in vitro data can be accepted instead.

For example, the requirement for in vivo data will be waived for different strengths of an IR drug product when:

(1) the drug product is in the same dosage form, but in a different strength;

(2) this different strength formulation is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval; and

(3) the new strength formulation meets an appropriate in vitro test as outlined in the regulations. In addition, to obtain a waiver for higher strengths, the sponsor should demonstrate that the pharmacokinetics over the therapeutic dose range are linear.

Characteristics that illustrate that formulations are proportionally similar include:

• All active and inactive ingredients are in identical proportions between different strengths (e.g., a tablet of 50-mg strength has exactly half of the active ingredients of a tablet of 100-mg strength and twice the active ingredients of a tablet of 25-mg strength).

• For drug substances with high potency where the amount of the active drug substance in the dosage form is relatively low (i.e., the amount of the active substance is less than 5 percent of the tablet core weight or the weight of the capsule content), then:

(1) the total weight of the dosage form remains nearly the same for all strengths (i.e., within plus or minus 10 percent of the total weight of the strength used in the BA study);

(2) the same inactive ingredients are used for all strengths; and

(3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.

• Bilayer tablets are considered a single formulation even though they consist of two separate layers with different compositions. In assessing the proportional similarity of different strengths of bilayer tablets, all components of both layers should be proportionally similar. The fact that only one layer is proportionally similar and the other is not indicates that the products (i.e., the whole tablet) are not proportionally similar.

• Active and inactive ingredients are not in identical proportions between different strengths as stated above, but the ratios of the inactive ingredients to the total weight of the dosage form are within the limits defined by the FDA's SUPAC-IR and SUPAC-MR

guidances for industry up to and including Level II changes.

B. In Vitro Studies Conducted in Support of BA

The FDA could determine that an in vitro approach is the most accurate, sensitive, and reproducible method to determine BA. Additional recommendations on the conduct of such studies is provided below.

1. IR Formulations (Capsules, Tablets, and Suspensions)

   In vitro data can be used to compare formulations of drug products under certain circumstances. If a sponsor seeks to determine the BA of IR formulations for capsules, tablets, and suspensions using in vitro data, the FDA recommends that sponsors generate dissolution profiles for all strengths using an appropriate dissolution method (see III.B.2 for more information on IVIVC). If the results indicate that the dissolution characteristics of the product are not dependent on the pH or product strength, then dissolution profiles in one medium are usually sufficient to waive the need to assess the in vivo BA. If these criteria are not met, the sponsor should collect dissolution data in at least three media (e.g., pH 1.2, 4.5, and 6.8). Similarity tests should be used to compare dissolution profiles from the different strengths of the product (see the FDA guidance entitled Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997)

a. Over-encapsulation of clinical trial formulations

   Binding of drug products used in clinical trials can be done by over-encapsulation of the dosage form. The sponsor should assess the impact of this over-encapsulation on the release of the drug substance from the drug product.

   Dissolution can be used to assess the impact of overencapsulation, provided that:

   (1) no excipients beyond those that are already in the dosage form are added to the capsule; and

   (2) the dissolution profiles between the over-encapsulated and nonover-encapsulated products are comparable in three media at pH 1.2, pH 4.5 and pH 6.8. However, if other excipients are added, then an in vivo study should be conducted unless the sponsor can provide a justification as to why the excipients added do not alter the BA of the over-encapsulated product. These recommendations apply equally to both the drug product under investigation as well as any product used as a comparator or reference product in the same clinical study. Enzymes could be added to the dissolution medium to better understand the effect of over-encapsulation on drug release.

b. Scale-up and postapproval changes

   Following approval, drug products can undergo formulation or manufacturing changes for a variety of reasons. Formulation changes can occur in components and composition, and manufacturing changes can occur in scale-up, manufacturing site, manufacturing process, or equipment. Depending on the possible impact of the manufacturing change on the release of the active ingredient from the drug product and the BA of the active ingredient, certain manufacturing changes for IR products can be approved based solely on the similarity of the dissolution profiles between the formulation after the change and the formulation before the change. Information on recommendations for using in vitro dissolution and in vivo BE studies for IR drug products in such circumstances is provided in the FDA's guidance entitled SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997). The same principles described in this guidance can be applied to pre-approval changes such as when the to-be-marketed formulation differs from the clinical trial formulation.

2. MR Formulations

   The use of in vitro data could be acceptable for MR drug products with specific postapproval changes. Specific information on the use of in vitro data for postapproval changes to MR drug products is delineated in the FDA's guidance entitled SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997). The same principles described in the guidance might also apply to pre-approval changes. Additional considerations for the use of in vitro data in support of determining a drug's BA are described below.

   a. Beaded capsules Per 21 CFR 320.24(b)(6), in vivo BA studies for higher strengths of beaded capsules (e.g., a strength that is

developed after initial BA studies of lower strengths) might not be necessary based on:
(1) the clinical safety or efficacy data of the proposed dose and the need for the higher strength;
(2) the linearity of the pharmacokinetics over the therapeutic dose range; and (3) whether the same dissolution procedures were used for all strengths and yielded similar dissolution results. The f_2 similarity test can be used to demonstrate similar profiles among the different strengths of the product. The sponsor can determine the in vivo BA of one or more lower strengths by comparing the dissolution profiles and conducting an in vivo BA study only on the highest strength (unless safety reasons preclude the administration of the highest strength to subjects). The dissolution profiles for each strength should be generated using the recommended dissolution method. If the dissolution method has not been finalized, dissolution profiles should be generated in at least three media (e.g., pH 1.2, 4.5, and 6.8).

b. Other MR dosage forms

For other MR dosage forms, the sponsor should conduct an in vivo BA study using the highest strength. The sponsor can determine the BA for lower strengths by comparing the dissolution profiles using f_2 evaluation when the drug product is in the same dosage form but in a different strength, and:
(1) the drug exhibits linear pharmacokinetics;
(2) the various strengths are proportionally similar in their active and inactive ingredients; and
(3) the mechanism of release of the drug is the same.

If the formulations of all the strengths are not compositionally proportional, in vitro data can be submitted for the middle strengths if the following data are acceptable:
(1) BA or BE data, as appropriate, for both the highest and the lowest strengths; and
(2) comparisons of in vitro multimedia dissolution profiles using f_2 evaluation. Alternatively, waivers can be granted for lower strengths that are not proportional to the highest strength if a dissolution safe space has been established for the drug product via either IVIVCs or IVIVRs combined with virtual BE.

SPECIAL TOPICS

Enantiomers Versus Racemates

During the development of a racemic drug product, the racemate should be measured in BA studies using an achiral assay. It could also be important to measure the individual enantiomers of the racemate to characterize the pharmacokinetics of the enantiomers. For the development of a specific enantiomer, chiral inversion should be assessed. Measuring individual enantiomers in BA is recommended only when all the following conditions are met:

- The enantiomers exhibit different PD characteristics
- The enantiomers exhibit different PK characteristics
- Primary efficacy and safety activities reside with the minor enantiomer
- At least one of the enantiomers exhibits nonlinear absorption (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) In such cases, the sponsor should apply BE criteria to the enantiomers separately.

Drug Products With Complex Mixtures as the Active Ingredients

Certain drug products can contain complex drug substances (i.e., active moieties or active ingredients that are mixtures of multiple synthetic or natural source components). The chemical structure or biological activity of some or all of the components of these complex drug substances might not be fully characterized. Quantification of all active or potentially active components in BA studies might not be possible. In such cases, sponsors should use a select number of components in BA studies. The criteria for selecting the components should typically include the amount of the moiety in the dosage form, the plasma or blood levels of the moiety, and the biological activity of the moiety. When PK approaches are not feasible to assess the rate and extent of absorption of a drug substance from a drug product, the sponsor can consider PD, clinical, or in vitro approaches. In such cases, sponsors should consult the appropriate review division on the approach and moieties for conducting BA studies.

Drugs With Long Half-Lives

In a BA or a PK study involving an IR, oral product with a long half-life (i.e., greater than or equal to 24 hours), characterization of the product's half-life should include blood sampling over an adequate period of time. To determine the BA of a drug product containing a drug with a long half-life, a single-dose crossover study should be conducted if an adequate washout period is used. If the crossover study is problematic, a study with a parallel design should be used. For either a crossover or parallel study, the sample collection time should ensure that

the drug product completely moves through the gastrointestinal tract so that the absorption of the drug substance (C_{max}) and a suitably truncated AUC (i.e., for drugs that do not exhibit flip-flop kinetics and drugs that do not have high intra-subject variability) can be used to characterize the peak and total drug exposures, respectively. In these cases, the sponsor should consult the appropriate review division on the duration of sampling and the choice of the PK measures for determining BA.

Orally Administered Drugs Intended for Local Action

Determining BA when the drug substance produces its effects by local action in the gastrointestinal tract can be achieved either by using pharmacokinetics, an acceptable PD endpoint, clinical efficacy and safety studies, or suitably designed and validated in vitro studies, as appropriate. In these cases, sponsors should consult the appropriate review division regarding the approach for assessing BA.

Narrow Therapeutic Index Drugs

In specific circumstances where knowledge of exposure measures of drugs (AUC or C_{max}) are critical for the safe and effective use of the drug product, or where therapeutic drug monitoring is an essential tool for drug product dosing, the acceptable criteria for demonstrating BE might need to be narrowed. Because of the complexities associated with narrow therapeutic index drugs, sponsors should contact the appropriate review division for additional information

APPENDIX A: GENERAL STUDY DESIGN AND DATA HANDLING

The following general approaches are recommended, recognizing that the elements can be adjusted for certain drug substances and drug products.

A. Study Conduct

• Generally, the BA or BE study should be conducted under fasted conditions (i.e., after an overnight fast of at least 10 hours).

• The test and reference products should be administered with about 8 ounces (240 milliliters) of water to the study subjects.

• Generally, the highest marketed strength should be administered as a single unit. If the highest strength is not deemed safe for healthy subjects, then the study can be performed in individuals with the disease or condition being studied, or a lower strength might be appropriate in healthy subjects. If bioanalytical sensitivity is a limitation, multiple units of the highest strength should be administered, if the total single dose remains within the labeled dose range, and the total dose is safe for administration to the study subjects.

B. Sample Collection and Sampling Times

Under normal circumstances, sponsors should collect blood, rather than urine or tissue. In most cases, the drug or metabolites should be measured in serum or plasma. However, in certain cases, such as when an assay of sufficient sensitivity cannot be developed for plasma, whole blood might be more appropriate for analysis. We recommend that sponsors draw blood samples at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, we recommend collecting 12 to 18 samples (including a pre-dose sample) per subject, per dose. This sampling should continue for at least three terminal elimination half-lives. For multiple-dose studies, sampling must occur at steady-state across the dose interval and include the beginning and the end of the interval. The exact timing for sample collection depends on the nature of the drug and the rate of input from the administered dosage form. The sample collection should be spaced in such a way that the Cmax of the drug in the blood and terminal elimination rate constant (λz) can be estimated accurately.

APPENDIX B: GUIDELINES FOR CONDUCTING FED OR FASTED STUDIES

For new IR drug products developed via the pathway under section 505(b)(1) of the FD&C Act for which BA is determined using a solution, IV, or a previously developed formulation as a reference, the BA study should be conducted under fasted conditions except when tolerability issues are anticipated in the fasted state. Additionally, the effect of food on the BA of the new drug product should be evaluated using a high-fat and high-calorie meal. If the objective is to evaluate the effect of other meal types, then other meals with different compositions can also be assessed in addition to the high-fat and high-calorie meal.

For new IR drug products developed under either section 505(b)(1) or 505(b)(2) of the FD&C Act for which relative BA is determined using an approved product as a reference:

• If the reference drug product is labeled to be taken under fasted conditions, then the test drug product should be compared under fasted conditions to the reference drug product for the relative BA comparison. In addition, evaluation of the effect of a high-fat meal on the new drug product can be useful

to support labeling of the test product. A three-way crossover study can be considered because it allows for the relevant comparisons (e.g., test fasted vs reference fasted and food-effect assessment) to be made directly.

• If the reference drug product is labeled to be taken without regard to meals, then the test and reference drug product should be compared under fasted conditions. In addition, the effect of a high-fat meal on the new drug product should be evaluated. Alternatively, the BA of the new drug product under fed conditions can be established by comparing the test product to the reference drug product both administered with a high-fat meal.

• If the reference drug product is labeled to be taken with food, then the test drug product should be compared under fed conditions. The fed conditions in this study should be the same as described in the labeling for the reference product. However, if no specific meal type is described in the reference product labeling, then the high-fat meal should be used for the comparison for the fed condition. In addition, the evaluation of the effect of a high-fat meal on the new drug product (test fed versus test fasted) can be useful to inform and support labeling of the test product. A three-way crossover study can be considered because it allows for the relevant comparisons to be made directly (e.g., test fed vs reference fed and food-effect assessment).

• If the reference drug product is labeled to be taken with food to avoid tolerability issues in the fasted state, then the BA for the test drug product should be evaluated under fed conditions according to the labeling instructions for the reference product.

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