Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Docket Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Lawrence J. Lesko at 301-594-5690.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2001
BP

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) Http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2001
BP

Table of Contents

Draft – Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance provides recommendations to sponsors and/or applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications. This guidance applies to both immediate-release and modified-release drug products. The guidance addresses how to meet the BA and BE requirements in 21 CFR 320, 314.50 (d) (3), and 314.94 (a) (7) as they apply to oral dosage forms. This guidance provides recommendations for food-effect BA and fed BE study design, data analysis, and product labeling, and also provides information on when food-effect BA and fed BE studies should be performed. It should be considered along with the FDA guidance for industry on *Bioavailablity and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (October 2000) and other relevant guidances.

This guidance is a revision of an October 1997 draft guidance entitled *Food-Effect Bioavailability and Bioequivalence Studies*. The important aspects of this revised guidance are the following:

[1] This guidance has been prepared by the Food Effect Working Group of the Biopharmaceutics Coordinating Committee in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

- It provides for waiver of BE studies under fed conditions when both test and reference listed drug (RLD) products are rapidly dissolving, have similar dissolution profiles, and contain a drug substance that is highly soluble and highly permeable (defined as Biopharmaceutics Classification System (BCS) Class 1) (see the FDA guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (August 2000) (BCS guidance)).

- It recommends that an equivalence approach be used for fasted vs. fed BA and fed BE comparisons, and that an average equivalence criterion be used to analyze C_{max} and AUC measurements. It proposes an equivalence limit of 80-125% for the analysis of C_{max} and AUC data (90% confidence interval (CI)) in food-effect BA studies as evidence of an absence of food effects and in fed BE studies to demonstrate the BE of a test and reference product.

II. BACKGROUND

A. Potential Mechanisms of Food Effects on BA

Food, in comparison to fasting conditions, can change the BA of a drug and can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by the following:

- Delay of gastric emptying
- Stimulation of bile flow
- Changes in gastrointestinal (GI) pH
- Increase in splanchnic blood flow
- Changes in luminal metabolism of a drug substance
- Physical or chemical interactions with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered immediately after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability (BA). In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. In this guidance, a high-calorie and high-fat meal is recommended for food-effect BA and fed BE studies.

B. Food Effects on Drug Products

Administration of drug products with food may change their BA through effects on either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which

food changes the BA of a drug product without performing specific mechanistic studies. The Agency believes that for many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) important food effects on BA are least likely to occur because absorption of drug substances in Class I is usually pH- and site-independent and insensitive to differences in dissolution.[2] However, food can influence BA when there is a high first-pass effect or extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. However, for rapidly dissolving formulations of BCS Class I drug substances, food can affect the time at which peak exposure occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. The food effect on T_{max} is expected to be similar for test and reference products.

For other immediate-release drug products (BCS Class II, III, and IV) and all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the direction and magnitude of food effects on BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a food-effect BA or fed BE study.

III. RECOMMENDATIONS FOR FOOD-EFFECT BA AND FED BE STUDIES

This section of the guidance provides recommendations on when food-effect BA studies should be conducted as part of INDs and NDAs, and when fed BE studies should be conducted as part of ANDAs. For postapproval changes in an approved immediate- or modified-release drug product that require in vivo redocumentation of BE under fasting conditions, fed BE studies are generally unnecessary.

A. Immediate-Release Drug Products

1. INDs/NDAs

Food-effect BA or fed BE studies of new chemical entities (NCEs) are usually conducted during the IND period to guide dosage form development, to select specific formulations, to help in the design of clinical efficacy studies, and to develop information for the CLINICAL PHARMACOLOGY and/or DOSAGE AND ADMINISTRATION sections of product labels. This guidance recommends that food-effect BA and fed BE studies be conducted early in the drug development process using the formulation to be employed in the clinical trials intended to provide primary evidence of efficacy and safety. If a sponsor makes

[2] To test the hypothesis that two rapidly dissolving drug products with a BCS Class I drug substance are unlikely to be bioinequivalent under fed conditions, the FDA is currently conducting clinical research studies at the University of Tennessee. The results of this research will be considered along with literature and in-house data to test this hypothesis as this guidance is being finalized.

changes in components, composition, and/or method of manufacture in the clinical trial formulation prior to approval, BE should be demonstrated between the to-be-marketed formulation and the clinical trial formulation. Sponsors may wish to use relevant principles described in the guidance for industry on *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR guidance) (November 1995) to determine if in vivo BE studies are recommended. These BE studies, if indicated, should generally be conducted under fasting conditions. When the fasting study does not establish BE, and food significantly affects the drug product's performance in vivo (BA), it is important to determine food effects on the to-be-marketed formulation.

2. ANDAs

In addition to a BE study under fasting conditions, a BE study under fed conditions is recommended for all orally administered immediate-release drug products, with the following exceptions:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I), as defined in the BCS guidance, or

- When the label of the RLD states that the product should be taken only on an empty stomach, or

- When the label of the RLD does not make any statements about the effect of food on absorption or administration.

B. Modified-Release Drug Products

Food-effect BA and fed BE studies, respectively, are recommended for all modified-release dosage forms because the BA of these products is likely to be altered by co-administration with meals.

1. INDs/NDAs

A study comparing the BA under fasting and fed conditions is recommended for all orally administered modified-release drug products.

When changes occur in components, composition, and/or method of manufacture between the to-be-marketed formulation and the primary clinical trial material, the sponsor may wish to use relevant principles described in the guidance for industry on *SUPAC-MR: Modified*

Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (June 1997) (SUPAC-MR guidance) to determine if documentation of in vivo BE is recommended. These BE studies, if indicated, should generally be conducted under fasting conditions. However, it is important to reassess food effects on the to-be-marketed formulation in certain circumstances when the fasting study does not establish BE and the administration with food significantly influences the drug product's in vivo BA.

2. ANDAs

In addition to a BE study under fasting conditions, a BE study under fed conditions is recommended for all orally administered modified-release drug products.

IV. STUDY CONSIDERATIONS

A. General Design

A randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design is recommended for studying the effects of food on the BA of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and immediately following a test meal (fed condition) in the other period. A similar two-treatment, two-period, two-sequence crossover design is recommended for a fed BE study except that the treatments should consist of both test and reference formulations administered immediately following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies. A sponsor can propose alternative study designs, but the scientific rationale and justification for these study designs should be provided in the study protocol. In studying modified-release dosage forms, consideration should be given to the possibility that co-administration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form, creating a potential safety risk for the study subjects.

B. Subject Selection

Both food-effect BA and fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also acceptable if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on BA to claim an absence of food effects, or to claim BE in a fed BE study. Typically, a minimum of 12 subjects should complete the food-effect BA and fed BE studies.

C. Dosage Strength

In general, the highest strength of a drug product should be tested in all food-effect BA and fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For ANDAs, the same lot and strength used in the fasting BE study should be tested in the fed BE study. For multiple strengths of modified-release dosage forms in ANDAs, if a fed BE study has been performed on the highest strength, there is no necessity for additional fed BE studies on other strengths, provided that the release mechanisms of the test product are identical and excipients are qualitatively the same for each strength.

D. Test Meal

Food-effect BA and fed BE studies should be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. A typical test meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. This test meal derives approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. Details of the test meal should be provided in the study report. If the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference. In NDAs, it is recognized that a sponsor can choose to conduct food-effect BA studies using meals with different combinations of fat, carbohydrate, and protein for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above.

E. Administration

Fasted Treatments: Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 hours, subjects should be given the recommended meal 30 minutes before dosing. The meal should be consumed over 30 minutes with administration of the drug product immediately after the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours

post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

F. Sample Collection

For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites, and sponsors should refer to the guidance on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* for recommendations on these issues. Consideration should be given to the possibility that co-administration of a dosage form with food can alter the time course of plasma drug concentrations so that fasting and fed studies can have different sample collection times.

V. DATA ANALYSIS AND LABELING

Food-effect BA studies may be exploratory and descriptive, or a sponsor may want to use a food-effect BA study to make a label claim.[3] An equivalence approach is recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. The following exposure measures for assessment of BA and BE should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- Total exposure, or area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant pharmacokinetic parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. Log-transformation of exposure measurements prior to analysis is recommended. The 90% CI should be provided for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} (see the FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence*). For IND or NDA food-effect BA studies, the fasted treatment serves as the reference. For ANDA fed BE studies, the RLD administered under fed condition serves as the reference treatment.

[3] Regulations on labeling requirements for a drug product submitted in an NDA can be found in 21 CFR part 201.

The effect of food on the absorption and BA of a drug product should be described in the CLINICAL PHARMACOLOGY section of the labeling. In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance (i.e., whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns, or when there is no important change in systemic exposure but there is a possibility that the drug substance causes GI irritation when taken without food).

For an NDA, a food effect on BA is indicated if the 90% CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80%-125% for either $AUC_{0-\infty}$ (AUC_{0-t}) or C_{max}. When the 90% CI fails to meet the limits of 80-125%, or when a food-effect BA study indicates a large food effect (defined as > 20% higher or lower peak or systemic exposure compared to fasting conditions), the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose-response (exposure-response) and/or pharmacokinetic-pharmacodynamic relationships of the drug under study. The clinical relevance of any difference in T_{max} and t_{lag} should also be indicated by the sponsor. The results of the food-effect BA study should be reported factually in the CLINICAL PHARMACOLOGY section of the labeling, and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the DOSAGE AND ADMINISTRATION section of the labeling. The following is an example of language for the package insert:

> *A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 hour before or 2 hours after a meal).*

No food effect on BA is indicated when the 90% CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80%-125% for $AUC_{0-\infty}$ (AUC_{0-t}) and C_{max}. In this case, a sponsor may make a specific claim in the CLINICAL PHARMACOLOGY or DOSAGE AND ADMINISTRATION section of the label that no food effect on BA is expected provided that the T_{max} values are also similar between the fasted and fed treatments. The following is an example of language for the package insert:

> *The C_{max} and AUC data from a food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. Therefore, [the drug product] may be taken without regard to meals.*

For an ANDA, BE of a test product to the RLD product under fed conditions is concluded when the 90% CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80-125% fo AUC and C_{max}. Although no criterion applies to T_{max}, the

T_{max} values for the test and reference products are expected to be comparable based on clinical relevance. The conclusion of bioequivalence under fed conditions indicates that with regard to food, the language in the package insert of the test product can be the same as the reference product.

VI. OTHER CONSIDERATIONS

A. Sprinkles

In NDAs, certain drug products (e.g., controlled-release capsules containing beads) can be recommended to be sprinkled on soft foods, such as applesauce, and swallowed without chewing. If the labeling indicates that the drug product may be sprinkled on soft food, an additional in vivo study should be performed by sprinkling the product on the soft food listed in the labeling and administering on an empty stomach (test treatment). For determining the relative BA of the test treatment, the reference treatment should be the drug product administered as an intact dosage form under fasting conditions.

In ANDAs, to demonstrate BE of the test to the RLD, both treatments should be sprinkled on one of the soft foods mentioned in the labeling. If there are questions about other foods, vehicles, design, or analysis of such BA and BE studies, the sponsors and/or applicants should contact the appropriate review division.

B. Special Vehicles

For NDAs, the labeling for certain oral solution products (e.g., cyclosporine oral solution, modified) recommends that the solution be mixed with a beverage prior to administration. The BA of these products can change when mixed with different beverages due to the formation of complex mixtures (e.g., an emulsion) and other physical-chemical and/or physiological factors. For INDs or NDAs, in vivo data supporting the use of each beverage recommended in the labeling should be provided unless the sponsor provides a scientific justification for waiving such studies. If there are questions on conducting studies in different beverages, NDA sponsors should contact the Office of Clinical Pharmacology and Biopharmaceutics.

For ANDAs, if a substantial difference in BA has been reported when the reference product is mixed with different beverages, and this difference is documented in the product labeling, sponsors may want to demonstrate BE of their product to the RLD using these various beverages. If there are questions on conducting studies in different beverages, ANDA sponsors should contact the Division of Bioequivalence in the Office of Generic Drugs.