Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

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

December 2002
BP

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

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)

December 2002
BP

Table of Contents

I. INTRODUCTION 1

II. BACKGROUND 1

A. Potential Mechanisms of Food Effects on BA 1

B. Food Effects on Drug Products 2

III. RECOMMENDATIONS FOR FOOD-EFFECT BA AND FED BE STUDIES 3

A. Immediate-Release Drug Products 3

B. Modified-Release Drug Products 4

IV. STUDY CONSIDERATIONS 4

A. General Design 4

B. Subject Selection 5

C. Dosage Strength 5

D. Test Meal 5

E. Administration 6

F. Sample Collection 6

V. DATA ANALYSIS AND LABELING 6

VI. OTHER CONSIDERATIONS 8

A. Sprinkles 8

B. Special Vehicles 8

Guidance For Industry[1]

Food-Effect Bioavailability and Fed Bioequivalence Studies

This guidance represents 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.

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 designs, data analysis, and product labeling. It also provides information on when food-effect BA and fed BE studies should be performed. [2]

II. BACKGROUND

Food effect BA studies are usually conducted for new drugs and drug products during the IND period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed BE studies, on the other hand, are conducted for ANDAs to demonstrate their bioequivalence to the reference listed drug (RLD) under fed conditions.

A. Potential Mechanisms of Food Effects on BA

[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).

[2] See also the guidance for industry on *Bioavailablity and Bioequivalence Studies for Orally Administered Drug Products C General Considerations*.

Food 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 various means, including

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly 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. 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. We recommend use of high-calorie and high-fat meals during food-effect BA and fed BE studies.

B. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting 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. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution.[3] However, for some drugs in this class, food can influence BA when there is a high first-pass effect, 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. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, we expect the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for 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 relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

---

[3] See the 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*.

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 requires in vivo redocumentation of BE under fasting conditions, fed BE studies are generally unnecessary.

A. Immediate-Release Drug Products

1. INDs/NDAs

We recommend that a food-effect BA study be conducted for all new chemical entities (NCEs) during the IND period.

Food-effect BA studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect BA information should be available to design clinical safety and efficacy studies and to provide information for the CLINICAL PHARMACOLOGY and/or DOSAGE AND ADMINISTRATION sections of product labels. If a sponsor makes 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) to determine if in vivo BE studies are recommended. These BE studies, if indicated, should generally be conducted under fasting conditions.

2. ANDAs

In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions 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) (see footnote 3), or

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

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

B. Modified-Release Drug Products

We recommend that food-effect BA and fed BE studies be performed for all modified-release dosage forms.

1. INDs/NDAs

We recommend a study comparing the BA under fasting and fed conditions 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* (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.

2. ANDAs

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

IV. STUDY CONSIDERATIONS

This section provides general considerations for designing food effect BA and fed BE studies. A sponsor may propose alternative study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g. different meals and different times of drug intake in relation to meals). 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 than intended, creating a potential safety risk for the study subjects.

A. General Design

We recommend a randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design 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 following a test meal

(fed condition) in the other period. We recommend a similar, two-treatment, two-period, two-sequence crossover design for a fed BE study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies.

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 appropriate 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 (see DATA ANALYSIS AND LABELING section). 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 intended to be marketed should be tested in 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 products with multiple strengths in ANDAs, if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on dissolution profile comparisons (for details see the guidance on *Bioavailablity and Bioequivalence Studies for Orally Administered Drug Products - General Considerations.*

D. Test Meal

We recommend that food-effect BA and fed BE studies 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 percent 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. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.[4] The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of 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 fats, carbohydrates, and proteins 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.

[4] An example test meal would be 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. 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.

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 start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of 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 fasted and fed treatments 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.[5] The following exposure measures and pharmacokinetic parameters 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 ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$)
- 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. An equivalence approach is

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

recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. Log-transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended. The 90 percent CI for the ratio of population geometric means between test and reference products should be provided for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} (see 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.

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, an absence of food effect on BA is not established if the 90 percent 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 percent for either $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}t}$ when appropriate) or C_{max}. When the 90 percent CI fails to meet the limits of 80-125 percent, 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 are examples 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)

> 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} was decreased 15% while the AUC remained unchanged. This decrease in exposure is not clinically significant, and therefore [the drug] could be taken without regards to meals.

An absence of food effect on BA is indicated when the 90 percent 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 percent for $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}t}$ when appropriate) and C_{max}. In this case, a sponsor can 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} differences between the fasted and fed treatments are not clinically relevant. 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 percent 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 percent for 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 BE 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, the labeling of certain drug products (e.g., controlled-release capsules containing beads) can recommend that the product be sprinkled on soft foods, such as applesauce, and swallowed without chewing. For the labeling to indicate that the drug product can be sprinkled on soft foods, additional in vivo relative BA studies should be performed by sprinkling the product on the soft foods to be listed in the labeling (test treatment) and comparing it to the product administered in the intact form (reference treatment), then administering both on an empty stomach.

In ANDAs, BE of the test to the RLD is demonstrated in a single dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The BE data should be analyzed using average BE and the 90 percent CI criteria should be used to declare BE. If there are questions about other foods, the design, or the analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

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 and other physical-chemical and/or physiological factors. NDA sponsors should contact the Office of Clinical Pharmacology and Biopharmaceutics to determine what data should be submitted to support labeling.

In ANDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be mixed with one of the beverages mentioned in the labeling. Sponsors

should provide evidence that BE differences would not be expected from the use of other listed vehicles. The BE data should be analyzed using average BE, and the 90 percent CI criteria should be used to declare BE. If there are questions about other vehicles, or the design or analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.