

Guidance for Industry

Food-Effect Bioavailability and Bioequivalence Studies

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY¹

Food-Effect Bioavailability and Bioequivalence Studies

I. INTRODUCTION

This document provides guidance to sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to conduct food-effect bioavailability (BA) and bioequivalence (BE) studies for oral immediate release (IR) or modified release (MR) dosage forms. BA and BE studies are generally conducted to meet regulatory requirements delineated in 21 CFR 320 (see also 314.94(a)(7)). They are performed during the preapproval phase for NDAs and ANDAs and also postapproval under certain circumstances. This guidance provides recommendations for study design, data analysis, and labeling, and indicates situations in which food-effect BA/BE studies may not be important.

II. DISCUSSION

A. Potential Causes of Food-Effects

Food induces changes in the physiology of the gastrointestinal tract. Physiological changes induced by food can result in delayed gastric emptying, stimulation of bile flow, changes in pH, and increase in splanchnic blood flow. Food can also alter luminal metabolism and physically or chemically interact with a drug substance.

The effects of food on BA and BE depend on the physico-chemical (solubility) and pharmacokinetic (site, rate, and extent of absorption, first pass metabolism) properties of the drug and on the dissolution of the drug substance from the drug product. The effects of coadministration of meals with drugs is maximal when the drug product is administered immediately after completion of a meal. The nutrient content, fluid volume, temperature, and caloric content of meals influence the magnitude of physiological changes that could

¹This guidance has been prepared by the Food-Effect Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on food-effect bioavailability and bioequivalence studies. 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 statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) <http://www.fda.gov/cder/guidance/index.htm>.

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affect drug absorption. Meals that are high in calories, fat, and density are likely to provide the greatest effects on BA.

B. Food-Effect BA Studies — Preapproval

Food-effect BA studies can be performed during the IND (Notice of Claimed Investigational Exemption for a New Drug) stage to determine whether coadministration of food affects the BA of the drug substance and/or the release of the drug substance from the drug product. If a food effect (e.g., a change in pharmacokinetic parameters or a change in safety and efficacy) is observed, the effect should be considered when designing clinical studies. The impact of any observed food effects and dosing instructions relative to meals should be specified in the labeling.

C. Food-Effect BE Studies — Preapproval

For ANDAs/AADAs during the preapproval period, food-effect BE studies could be important to ensure that the effects of food on the ANDA/AADA formulation are the same as that on the formulation of the reference listed drug (RLD).

D. Food-Effect BE Studies — Postapproval

For both NDAs and ANDAs/AADAs, the performance of food-effect BE studies should be considered during the postapproval period when scale-up and postapproval changes (SUPAC) are of such magnitude that redocumentation of BE is considered important under both fed and fasted conditions. Generally, postapproval food-effect studies will be important only for changes in components and/or composition and for major changes in the manufacturing process (referred to subsequently in this guidance as formulation and processing factors).

E. When Food-Effect BA/BE Studies May Not Be Important

Once a primary food-effect BA study has been conducted, subsequent food-effect studies during the IND phase, food-effect BE studies for ANDAs/AADAs and postapproval food-effect BE studies for NDAs, ANDAs/AADAs may not always be important. Specifically, if the effect of food is primarily on absorption of the drug substance, subsequent food effect BA/BE studies should be performed only when the effect of food is likely to arise from formulation and/or processing factors. Also, for ANDAs/AADAs, food-effect studies should not be performed routinely based solely on a labeling statement for the RLD describing a food effect or specifying administration in relation to meals. Certain drug substance and IR drug product characteristics, referred to subsequently in this guidance as diagnostic factors, can be used to determine whether additional food-effect

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studies are important. For a drug substance, these diagnostic factors include (1) high drug solubility across the intended dose range; (2) high drug permeability across the intended dose range (e.g., oral absorption greater than 90%); and (3) minimal or no effect of inactive ingredients on absorption of the drug substance in the fasted state (i.e., BE shown between the test formulation and a simple solution or suspension). For a drug product, the diagnostic factors include (1) rapidly dissolving drug product (e.g., Case A specifications in SUPAC IR) and (2) in-vitro dissolution characteristics similar in different pH media and rotation speeds for basket or paddle in USP 23 Apparatus 1 or 2. These characteristics should be present to obviate redocumentation of food-effect BA or BE. If all these characteristics are not present, sponsors should provide justification for why a food-effect BA or BE study is not important.

III. STUDY CONSIDERATIONS

Primary studies to assess the effect of food on the BA/BE of the drug substance and the release of the drug substance from the drug product should be conducted according to the design proposed in this guidance. Additional studies using different meals and different times of drug intake in relation to meals may be important to amplify the information from these initial studies and to provide optimal labeling statements for dosage and administration. Alternate approaches can be used with appropriate justification.

A. General Design

A randomized, balanced, single-dose, two-treatment, two-period, two-sequence crossover is recommended for food-effect BA studies designed to assess the effects of food on either the drug substance/and or the release of the drug substance from the drug product. The formulation to be tested should be administered under fasted conditions in one treatment and immediately following a test meal (fed condition) for the other treatment. The recommended study design should be adjusted if the primary purpose of the study is to ascertain the effects of food on the absorption of the drug substance. In this case, the drug substance can be administered in a simple solution or suspension formulation. A similar design is recommended for a food-effect BE study except that the treatments consist of the test formulation and the RLD formulation administered under fed conditions. An adequate washout period should separate the two treatments.

B. Subject Selection

Food-effect BA and BE studies are usually carried out in healthy human volunteers. An adequate number of subjects should complete the study so as to achieve sufficient power

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for appropriate statistical assessment (see section on Data and Statistical Analysis, below), but should not be fewer than 12.

C. Dosage Form Selection

NDAs for IR Products: Food-effect information should be provided on the to-be-marketed formulation. A food-effect study conducted early in drug development could be useful to optimize dosing in clinical trials. However, early studies often use a formulation that is different from that to-be-marketed. In such cases, using the above-described diagnostic factors, the NDA sponsor should assess whether an identified food effect suggests that further studies should be performed with subsequent changes in formulation and/or processing. If it is reasonable to conclude that the food effect is due to the drug substance and not the formulation and/or processing factors, additional food-effect studies may not be important, even with major formulation and/or process changes for IR dosage forms.

ANDAs for IR Products: When a food effect is believed to be related to the drug substance and not the formulation and/or processing factors, ANDA food-effect studies on IR formulations may not be important. When such information is unavailable, the test and RLD products should be compared under fed conditions in addition to the comparison under fasted condition. Once drug-specific guidances are developed, they will provide suggestions for the need of food-effect BE studies. As noted, scientific information should lead to a need for a food-effect BE study, not the presence or absence of a food-effect statement in labeling of the RLD.

NDAs for MR Products: Information on food effects should be obtained for the to-be-marketed formulations of all NDAs for MR products. Additional studies during MR formulation development can be undertaken by sponsors who wish to distinguish between food effects due to drug substance versus effects due to formulation and/or processing factors. Major postapproval changes in formulation and/or processing leading to a recommendation for a fasted BE study (see SUPAC-MR) should be accompanied by a food-effect BE study. Sponsors should provide justification for not conducting this postapproval study.

ANDAs for MR Products: All ANDAs for MR formulations should establish, in addition to BE under fasted conditions, BE to the RLD formulation under fed conditions.² Major

²See guidance document entitled *Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing*. This 1993 guidance was developed by the Office of Generic Drugs to assist sponsors in the conduct of biopharmaceutics studies for modified (extended/controlled) release ANDAs/AADAs. Note: the Food-Effect Bioavailability and Bioequivalence Studies guidance replaces the recommendation in the 1993 guidance for a

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postapproval changes in formulation and/or processing involving a fasted BE study should be accompanied by a food-effect BE study. Sponsors should provide justification for not conducting this postapproval study.

Strength: Generally, the highest strength of a product should be tested in food-effect BA and BE studies. In some cases, clinical safety concerns could warrant use of lower strengths of the dosage form. For ANDAs, the lot and strength tested in the pivotal BE fasted study should be tested in the food-effect BE study. When multiple strengths of MR drug products are intended for marketing and the food-effect BA or BE study is performed on one of these strengths, in-vitro dissolution testing should be conducted for all other strengths in three different pH media. Similarity of dissolution should be established in accordance with the f2 test specified in SUPAC guidance documents. Lack of similarity of dissolution could indicate that additional food-effect studies should be performed using other strengths.

D. Test Meal

The primary food-effect BA and BE study should be conducted under conditions expected to provide maximal perturbation due to presence of food in the GI tract. A high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) breakfast is therefore recommended as a test meal for food-effect BA and BE studies. A representative example is 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 ounces of whole milk (i.e., approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calories). Alternative meals with equivalent nutritional content can be used. Details of the meal should be recorded prior to the study and provided in the study report. The sponsor should provide a scientific rationale if the selected meal is not high in calories and fat.

E. Administration

Fasted treatments: Following an overnight fast of at least 10 hours, subjects should take the drug product with 180 ml (6 fl oz) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed *ad libitum* after 2 hours. Scheduled standardized meals should be served throughout the remaining study period.

Fed treatments: Following an overnight fast of at least 10 hours, subjects should be served the test meal and ingest this meal within 30 minutes. The drug product should be

three-treatment study (fed/test, fed/reference, fasting/test) with a two-treatment food-effect study (fed/test, fed/reference). Sponsors of ANDAs/AADAs can begin using the food-effect approach in this guidance once the guidance is finalized in the expectation that the 1993 guidance will be updated.

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administered with 180 ml (6 fl oz) of water immediately (within 5 minutes) after completion of the meal. No food should be allowed for at least 4 hours post-dose. Water can be allowed *ad libitum* after 2 hours. Subjects should be served scheduled standardized meals throughout the remaining study period.

F. Sample Collection

For both treatment periods, timed biological fluid samples should be collected from the subjects to permit characterization of the complete plasma concentration-time profile for drug and/or metabolites. Caution should be used when studying MR dosage forms (e.g., enteric coated products) where coadministration with food can delay *in vivo* drug release. In such instances, sampling times should be adjusted to obtain the complete plasma concentration-time profile.

G. Data and Statistical Analysis

The following measurements should be obtained from the resulting concentration-time profiles:

- Area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})
- Peak concentration (C_{max})
- Time to peak concentration (t_{max}), and
- Lag-time (t_{lag}) for delayed release products

Individual subject parameters, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation, 90% confidence intervals [CI]) should be reported. In food-effect BA studies, the fasted treatment serves as the reference. In food-effect BE studies, the RLD product administered under fed conditions serves as the reference.

The results for food-effect BA studies will be evaluated according to the following options:

Food Effect Absent: Absence of a food effect will be concluded when the 90% CI for the ratio of means (population geometric means based on log-transformed data) of fed and fasted treatments fall within 80%-125% for AUC and 70%-143% for C_{max} .

Food Effect Documented: A food effect will be concluded when the 90% CI for the ratio of means (population geometric means based on log-transformed data) of fed and fasted treatments fall outside 80%-125% for AUC and 70%-143% for C_{max} . Clinical relevance of the observed magnitude of effect should be indicated by the sponsor.

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Food Effect Indeterminant: When a food effect is neither absent nor documented according to the above criteria, a food effect should be concluded to be indeterminant. Clinical relevance of the observed magnitude of effect should be indicated by the sponsor.

For NDAs, clinical relevance of a possible (indeterminant) or documented food effect should be addressed by sponsors in the product labeling (see section on NDA labeling, below). For ANDAs, an equivalent food effect will be concluded when the 90% CI for the ratio of means (population geometric means based on log-transformed data) of the test and RLD fall within 80-125% for AUC and 70-143% for C_{\max} . If these CI criteria are not satisfied, the test formulation might not be considered equivalent to and interchangeable with the RLD. For both NDAs and ANDAs, clinical relevance of any change in t_{\max} and t_{lag} should be considered.

IV. NDA LABELING

Regulations pertaining to labeling requirements can be found in 21 CFR 201. Some general recommendations on how to address food effects in the labeling in NDAs are discussed below.

A. Food Effect Absent

When absence of a food effect is documented, product labeling should state that a food effect was not present. If coadministration with food is otherwise clinically beneficial, the DOSAGE AND ADMINISTRATION section of the labeling should provide appropriate instructions.

B. Food Effect Documented

When a food effect is documented, the DOSAGE AND ADMINISTRATION section of the labeling should indicate the magnitude of food-effect on AUC and C_{\max} and discuss the clinical relevance.

C. Food Effect Indeterminant

When a food effect is indeterminant, the DOSAGE AND ADMINISTRATION section of the labeling should indicate the magnitude of the food effect on AUC and C_{\max} (unless population mean differences are $\leq 10\%$) and the clinical relevance should be discussed.

In general, the DOSAGE AND ADMINISTRATION section of the labeling should provide the optimal instructions for drug administration in relation to food.