Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology at CDER_OCP_GPT.

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

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Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to sponsors planning to conduct food-effect (FE) studies for orally administered drug products as part of investigational new drug applications (INDs), new drug applications (NDAs), and supplements to these applications. This guidance revises and replaces part of the 2002 FDA guidance for industry entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies*. Information on fed bioequivalence (BE) studies to be submitted in abbreviated new drug applications (ANDAs) is now found in the FDA draft guidance for industry entitled *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[2] Specific recommendations concerning fed comparability trials are now described in the FDA draft guidance for industry entitled *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*.[3]

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

II. BACKGROUND

[1] This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic

[3] When final, this guidance will represent the FDA's current thinking on this topic.

Food-drug interactions can have a significant impact on the safety and efficacy of the drug. These effects can be manifested in different ways. In some cases, co-administration of a drug with food can increase the systemic exposure of the drug, leading to improved efficacy or higher rates of adverse reactions. In other cases, administration of a drug with food can lower the systemic absorption of a drug, thereby reducing the efficacy. Hence, assessing the effect of food on the absorption of a drug is critical to optimize the safety and efficacy of the product and to determine optimum instructions for drug administration in relation to food. Because diets vary with respect to the amount and type of food, and maintaining strict control over the daily content of food can be difficult, developing drug formulations that are not affected by food is strongly encouraged. However, when developing such formulations is not possible, well-conducted FE trials can inform how, when, and why drugs should or should not be administered with food.

During new drug development, pharmacokinetic studies to assess the effect of food on the systemic exposure of the drug are conducted to determine: (1) if, and to what extent, food impacts the systemic exposure of the drug; (2) whether food increases or decreases the variability of the systemic exposure of the drug; and (3) if the effect of food is different across meals with different fat or caloric contents. For example, the absorption of a drug can increase when the drug is given with a high-fat meal, while a low-fat meal has inconsequential effects on the absorption of the same drug. To provide dosing instructions in relation to food, FE studies that include additional meal types that may not result in a clinically relevant food effect can be beneficial and provide useful labeling information.

It is important to have a detailed understanding of the exposure-response relationships of the drug to interpret the results of FE studies. For example, the observed increase or decrease in the systemic exposures of some drugs in the presence of food may not be clinically relevant based on exposure-response information. If appropriately conducted FE studies indicate that food does not have a clinically significant impact on the pharmacokinetics (PK) of the drug, the sponsor can conduct pivotal trials without regard to food, and the labeling can state that the drug can be taken with or without food.

In other cases, the clinical pharmacology characteristics of the drug may suggest that it should be administered only under fasted conditions (e.g., when higher exposures under fed conditions raise the risk of a clinically significant adverse reaction). In such cases, the drug should be administered without food in clinical trials, and the sponsor should determine a realistic interval between drug administration and meals that patients can practically implement to include in the product labeling. On the other hand, some drugs have undesired side effects that can be alleviated when taken with a meal. For example, drugs that cause localized gastric irritation can adversely impact patient compliance or lead to loss of the dose from vomiting. In such cases, administration of drugs with food can often alleviate the gastric discomfort and improve compliance. However, if food also has a significant effect on the exposure of the drug, then the evaluation of the effect of additional meal types on the PK of the drug may be helpful. Lastly, in some circumstances, food may increase absorption, and co-administration with food may be the only practical means of enhancing the efficacy of the drug in patients.

III. RECOMMENDATIONS FOR FE STUDIES

Sponsors should conduct FE studies for all new chemical entities and should consider conducting FE studies in other scenarios, such as but not limited to, modified-release or combination products of new or approved drugs. Sponsors are strongly encouraged to engage FDA staff early in the development of a new drug regarding the strategy and details of FE studies. The general recommendations for these FE studies are as follows:

- Sponsors should assess the effect of food on the PK of a new drug early in development to inform the overall drug development program and final product labeling.

- Sponsors should test the effect of food on a new drug in clinical trials (see section IV) *before* conducting the pivotal safety and efficacy trials to provide informed decisions regarding dosing with respect to food.

- The sponsor should conduct a pivotal FE trial using the to-be-marketed formulation when it is different than the clinical trial formulation used in the pivotal safety and efficacy trial (see the FDA guidance for industry entitled *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*[4] for more information).

- In some situations, sponsors should assess the effects of different types of meals on a new drug, as discussed above.

- When the efficacy or safety of a new drug is adversely impacted by food, and fasted dosing is necessary, the sponsor should conduct FE studies to determine a realistic time interval between drug administration and meals, which depends on the characteristics of the drug (e.g., 2 hours before a meal, and 1 hour after).

IV. TIMING OF FE STUDIES

This section of the guidance provides recommendations on when FE studies should be conducted during the development of a new drug:

- Preliminary assessments of the effects of food on a new drug can occur in phase 1 pilot trials (e.g., as part of the first-in-human trials (see section V)) and help determine whether a drug should be administered with food in clinical trials until a to-be-marketed formulation is identified.

- The sponsor should also conduct a pivotal FE study using the formulation to be used in the pivotal efficacy and safety trial and in some cases the to-be-marketed formulation, if different, to guide dosing in clinical trials and provide adequate labeling instructions (see section V and the FDA guidance for industry entitled *Bioavailability Studies Submitted in*

[4] When final, this guidance will represent the FDA's current thinking on this topic.

NDAs or INDs — General Considerations[5]).

V. CONSIDERATIONS FOR DESIGNING FE STUDIES

This section provides general considerations for designing FE studies. Sponsors can propose alternative trial designs and data analyses. The sponsor should provide the scientific rationale and justifications for any alternative trial designs and analyses in the study protocol.

A. Pilot Studies

The sponsor should conduct a pilot study to provide a preliminary assessment of the effect of a high-fat meal on the systemic exposure of the drug. To ensure the safety of the subject population, sponsors should carefully choose the dose for the FE assessment to account for any potential significant effects of food on the exposure of the drug that might increase the number or severity of adverse events.

B. Pivotal Studies

The sponsor should use a randomized, balanced, single-dose, two-treatment (i.e., fed versus fasted), two-period, crossover design to study the effects of food on either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach during one period and the high-fat test meal during the alternate period. For other types of meals, see section C below. A washout period of five elimination half-lives of the drug should separate the treatments in the FE study.

For drugs with long elimination half-lives (i.e., longer than 24 hours), a single-dose, parallel study design can be more practical. In these studies, the sponsor should administer each treatment (i.e., fasted, food-drug combination) to a separate group of subjects with similar demographics.

The sponsor should enroll an adequate number of subjects to sufficiently characterize the effect of food on the PK of the drug. The pharmacokinetic variability of the drug will affect the sample size for each group. At a minimum, 12 subjects should be enrolled in each treatment arm.

If a conventional FE study with rich pharmacokinetic sampling cannot be performed, the sponsor should consider conducting a well-designed and well-controlled population pharmacokinetic study to assess the potential effects of food on a new drug. However, these types of analyses are often hampered by a lack of reliable information regarding drug dosing relative to the type and amount of food as well as adequate sampling of each subject's drug levels to sufficiently characterize the absorption phase of the drug. Sponsors are strongly encouraged to seek FDA input early in the conceptual stage of population pharmacokinetic studies that assess the effect of food on a drug to ensure careful planning and execution of such studies.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

C. Types of Meals to Evaluate

For all orally administered drugs under development, an FE study with a high-fat meal should be conducted. Table 1 provides the definition of various test meals:

Table 1. Test Meal Definitions

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat[6]	800-1000	500-600	55-65	50
Low-Fat[7]	400-500	100-125	11-14	25

The physiological conditions induced by a high-fat meal generally provide the greatest effects on gastrointestinal physiology and the maximum effects on the systemic availability of the drug. For some drugs, the effect observed with a high-fat meal is not observed with a low-fat meal. When drug administration with a high-fat meal causes unacceptable toxicity or a loss of drug efficacy, a low-fat meal can have less or no impact on systemic exposures, improve patient compliance, and alleviate localized gastric irritation. In these circumstances, administration of the drug with a low-fat meal may be more advantageous to patients.

The sponsor should provide a description of the meal, the caloric and content breakdown (carbohydrates, proteins and fat), and the type of fat (e.g., percent saturated fat and percent unsaturated fat) in the study report. Examples of high- and low-fat meals are provided in the Appendices and can help guide trial design and product labeling.

D. Subject Selection

Sponsors can conduct FE studies in healthy adult subjects. Subjects from the patient population can also be appropriate if safety concerns preclude the enrollment of healthy subjects, or if differential effects of food on the drug are expected in the target patient population as compared to healthy subjects because of the underlying disease condition.

The sponsor should enroll both male and female subjects in the FE study unless the indication is specific to one sex (e.g., oral contraceptives), or if safety concerns preclude the enrollment of one sex (e.g., if the drug is a teratogen, women of child-bearing age should be excluded). Subjects in FE studies should have normal renal and hepatic function. Sponsors should exclude subjects if they cannot refrain from using concomitant drugs that could confound the results of the FE study (e.g., drugs that can alter the absorption of other drugs by affecting gastrointestinal motility or by changing the gastric pH as well as drugs that can increase or decrease the metabolism and excretion of the investigational drug).

[6] See Appendix1: Composition of a High-Fat Meal

[7] See Appendix2: Composition of a Low-Fat Meal

E. Test Doses

The sponsor should use the clinically recommended dose in the pivotal FE study. When several doses of a drug that exhibit linear PK will be marketed, the sponsor should use the highest clinically recommended dose unless safety concerns necessitate a lower dose. When it is unsafe to administer the therapeutic dose to healthy subjects, the sponsor can test the highest strength of the drug formulation in lieu of the highest dose, as long as the PK of the drug over the therapeutic range are linear. For drugs with nonlinear PK across the therapeutic dose range, the sponsor should conduct single-dose FE studies using both the high and low doses listed in the product labeling

F. Administration

1. Fasted Conditions

Following an overnight fast of at least 10 hours, investigators should administer the drug product to study subjects with 240 mL (i.e., 8 fluid ounces) of water. Additional water is permitted ad lib except for the period 1 hour before to 1 hour after administration of the drug product. The study subjects should not consume any food for at least 4 hours after the dose. Subjects should receive standardized meals scheduled at the same time throughout the study.

2. Fed Conditions

Following an overnight fast of at least 10 hours, the study subjects should start the recommended meal 30 minutes before administration of the drug product. Trial subjects should eat this meal in 30 minutes or less. The study subjects should take the drug product with 240 mL (8 fluid ounces) of water. Additional water is allowed ad lib except for 1 hour before and 1 hour after drug administration. No food is allowed for at least 4 hours after the dose.

3. Modified Fasted Condition

When fasted dosing is necessary because food can significantly increase or decrease the exposure of the drug, the standard, overnight, fasted, test condition may not be practical for patient treatment. Furthermore, the results of the overnight fasted condition may not be applicable to shorter periods of fasting in patients. To provide food-drug labeling instructions (e.g., no food should be consumed *X hours before* or *Y hours after* drug administration) for such products, the sponsor should conduct FE studies with appropriate separation times between drug administration and food consumption. The sponsor should provide pharmacokinetic data to support pragmatic labeling instructions to prevent food-drug interactions, taking into consideration the frequency of dosing, the patient demographics, and the disease condition, etc.

G. Sample Collection

For both fasted and fed treatment periods, the sponsor should collect samples in a biological matrix (e.g. plasma) from the study subjects to characterize the complete plasma concentration versus time profile for the parent drug (e.g., 12-18 samples per subject per period). The sponsor can use

different sample collection times for the fasted and fed treatments when co-administration of a drug with food is expected to alter the time course of drug concentrations in the plasma. To determine whether to measure other moieties in the plasma, such as active metabolites, sponsors should refer to the FDA guidance for industry entitled *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*.[8]

VI. OTHER CONSIDERATIONS

A. FE Study Waivers

Biopharmaceutical Classification 1 (BCS class 1) drugs are typically highly soluble, highly permeable, and rapidly dissolving compounds that are unaffected by food. Internal FDA data indicate that more than 80 percent of BCS class 1 immediate-release drugs are not affected by high-fat meals; therefore, the labeling for these drugs states that they can be administered without regard to food. The remaining BCS class 1 drugs are subject to high first-pass metabolism effects and can be affected by meals. The FDA may waive the requirement for sponsors to conduct an FE study for drugs that are designated as BCS class 1 (i.e., high solubility, high permeability) immediate-release drugs as defined in the FDA guidance for industry entitled *Waiver of In Vivo Bioavailability and Bioequivalence (BE) Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* that also have a high bioavailability ($F \geq 0.85$). Sponsors should consult the FDA regarding the feasibility of an FE study waiver.

B. Drug Products Labeled for Administration With Soft Foods

The labeling of certain drugs (e.g., oral granules, or extended-release capsules) recommends that the product be sprinkled on soft foods (e.g., applesauce, pudding, etc.). Some formulations should be swallowed without chewing. For the labeling to indicate that the drug can be sprinkled on soft foods, the sponsor should perform additional in vivo, relative bioavailability studies using the soft foods listed in the labeling (i.e., test treatment). All soft foods intended for labeling should be tested. When the product is also labeled for administration as an intact dosage form (tablets, capsules), the drug administered in the intact form taken with the soft food (i.e., reference treatment) should be compared to the test treatment.

C. Drug Products Labeled for Administration With Special Vehicles

The labeling of certain oral products (e.g., cyclosporine oral solution) recommends that the product be mixed with a beverage before administration. The bioavailability of these products can change when mixed with different beverages because of the formation of complex mixtures and other physical, chemical, or physiological factors. Sponsors should contact the FDA to determine what data should be submitted to support the labeling of these products.

D. Specific Populations

[8] When final, this guidance will represent the FDA's current thinking on this topic.

298 *1. Geriatrics*
299
300 The FDA does not recommend a dedicated FE study in an elderly population (i.e., patients
301 greater than 65 years old). The incidence of certain diseases (e.g., gastro-esophageal reflux
302 disease) increases with age, which can alter the bioavailability of drugs. However, these
303 diseases do not influence the effect of food on the bioavailability of the drug in an age-
304 dependent manner.
305
306 *2. Pediatrics*
307
308 When a new pediatric formulation is developed, the sponsor should conduct a new FE study
309 with the pediatric formulation in adults and then extrapolate the results to the pediatric
310 population. Sponsors can use foods and quantities of food that are commonly consumed with
311 drugs in a particular pediatric population (e.g., formula for infants and jelly, pudding, or apple
312 sauce for toddlers).
313
314 When the same to-be-marketed formulation that is approved for use in adults is approved for use
315 in a pediatric population, a separate FE study is not necessary. Furthermore, a separate FE study
316 may not be necessary if a pediatric formulation is very similar to the adult formulation (e.g., a
317 reduced strength tablet) and if the pediatric formulation is approved based on in vitro dissolution
318 tests.
319
320 **E. Fixed-Combination Drug Products**
321
322 The effect of food on each active ingredient or therapeutic drug moiety in a combination drug
323 product can be different from the effect of food when each active drug ingredient or therapeutic
324 drug moiety is administered alone. Therefore, the sponsor should assess the effect of food on the
325 various active ingredients or therapeutic drug moieties of the combination drug product after
326 administration of the combination drug product.
327
328
329 **VII. DATA ANALYSES AND LABELING**
330
331 **A. Data Analyses**
332
333 The following exposure measures and pharmacokinetic parameters should be derived from all FE
334 studies and reported:
335
336 • The total exposure of the drug, or area under the concentration-time curve ($AUC_{0\text{-}INF}$,
337 $AUC_{0\text{-}t}$)
338
339 • The partial exposure of the drug, or area -under-the-concentration-time curve (pAUC) for
340 MR products
341
342 • The peak concentration of the drug (C_{max})
343

- The time to the peak concentration of the drug (T_{max})
- The delay in achieving T_{max} (t_{lag})
- The terminal elimination half-life of the drug ($t_{1/2}$)
- The apparent clearance (Cl/F)
- The apparent volume of distribution (Vd/F)

Individual subject measurements as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation, ranges) should be reported.

When an FE bioavailability trial is conducted to assess changes in formulations, an equivalence approach is recommended (refer to the FDA guidance for industry entitled *Bioavailability Studies Submitted in NDAs or INDs—General Considerations*[9]). To make a claim of no food effect, the data should be analyzed using an average criterion, with the fasted treatment arm serving as the reference.

Exposure measurements (AUC and C_{max}) should be log-transformed. The 90 percent confidence interval for the ratio of the population geometric means between the fed and fasted conditions should be provided for $AUC_{0\text{-}INF}$, $AUC_{0\text{-}t}$, and C_{max}. An absence of a food effect on bioavailability is established if the 90 percent confidence interval for the ratio of the 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}, unless other criteria based on the established exposure-response relationships for the drug are more appropriate (refer to the FDA guidance for industry entitled *Statistical Approaches to Establishing Bioequivalence*). When the 90 percent confidence interval for the ratio of the population geometric means of either $AUC_{0\text{-}INF}$ ($AUC_{0\text{-}t}$ when appropriate) and C_{max} between fed and fasted treatments 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 the drug's exposure-response relationships. The clinical relevance of any difference in T_{max} and t_{lag} should also be indicated by the sponsor.

B. Labeling

Product labeling should include a summary of essential information pertaining to the effect of food on the PK and PD of the drug (if known) that is needed for the safe and effective use of the drug. See the FDA's guidance for industry entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*. The effect of food on the absorption of orally administered drugs should be described under a subheading called "Effect of Food" under the "Absorption" heading in the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section. The "Effect of Food" subheading includes detailed information that informs actionable recommendations that are described in the DOSAGE AND

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ADMINISTRATION section of labeling as well as other sections of labeling when pertinent (e.g., WARNINGS AND PRECAUTIONS, PATIENT COUNSELING INFORMATION). See Appendix 3 of this guidance for examples of incorporating FE information in labeling.

APPENDIX 1. COMPOSITION OF A HIGH-FAT MEAL*

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600
An Example of a High-Fat Breakfast	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk.

*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.

APPENDIX 2. COMPOSITION OF A LOW-FAT MEAL

Total Calories	400-500
Fat (g)	11-14
Percent Calories from Fat	25
An Example of a Low-Fat Breakfast*	• Eight ounces milk (1 percent fat) • One boiled egg • One packet flavored instant oatmeal made with water

*This low-fat breakfast contains 387 calories and has 10 grams of fat

APPENDIX 3. LABELING EXAMPLES

Example 1

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage for DRUG-X is 500 mg orally once daily on an empty stomach. Do not consume food 2 hours before each dose or 1 hour after each dose *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

…

12.3 Pharmacokinetics

Absorption

Effect of Food

Following administration of DRUG-X to healthy volunteers, the C_{max} increased 57% and the AUC increased 45% with a high-fat meal (1000 calories, 50% fat; compared to fasted conditions *[see Dosage and Administration (2.1)]*.

Example 2

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage for DRUG-X is 250 mg orally twice daily with a low-fat meal (400 calories, 25% fat) or on an empty stomach Do not take DRUG-X with high fat meals (1000 calories, 50% fat) *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

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12.3 Pharmacokinetics

Absorption

Effect of Food

Following administration of DRUG-X to healthy volunteers, the C_{max} increased 74%, and the AUC increased 87% with a high-fat meal (1000 calories, 50% fat) compared to fasted conditions *[see Dosage and Administration (2.1)]*.

Following administration of DRUG-X in healthy volunteers, the C_{max} increased 12%, and the AUC increased 14% with a low-fat meal (400 calories, 25% fat) compared to fasted conditions. These exposure changes are not clinically-significant.

Example 3

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage for DRUG-X is 400 mg orally once daily with meals (i.e., 400-1000 calories, 25-50% fat) *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

…

12.3 Pharmacokinetics

Absorption

Effect of Food

Following administration of DRUG-X to healthy volunteers, the C_{max} increased 15%, and the AUC increased 65% with a low-fat meal (400 calories, 25% fat) compared to fasted conditions. The C_{max} increased 17%, and the AUC increased 73% with a high-fat meal (1000 calories, 50% fat) compared to fasted conditions *[see Dosage and Administration (2.1)]*.

Example 4

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage for DRUG-X is 800 mg orally twice daily with or without meals *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

…

12.3 Pharmacokinetics

Absorption

Effect of Food

Following administration of DRUG-X to healthy volunteers, the C_{max} decreased 15%, while the AUC remained unchanged with a high-fat meal (1000 calories, 50% fat) compared to fasted conditions. This concentration decrease is not clinically significant *[see Dosage and Administration (2.1)]*.