Clinical Pharmacology Considerations for Food Effect Studies: An Overview of the FDA Food Effect Guidance

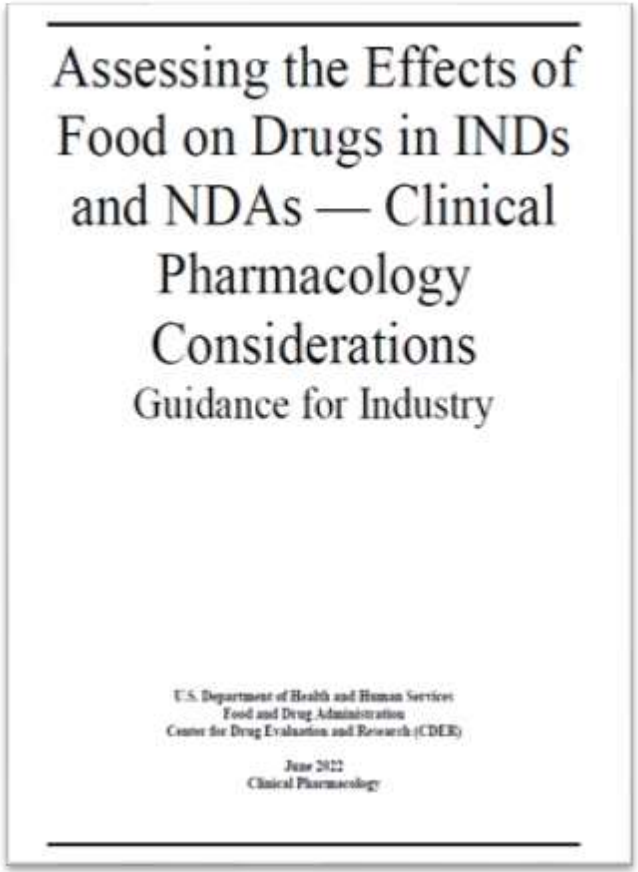
Vikram Arya, Ph.D., FCP
Associate Director for Therapeutic Review (ADTR)
Division of Infectious Disease Pharmacology, Office of Clinical Pharmacology
CDER | US FDA

FDA SBIA Webinar "Overview: Clinical Pharmacology Considerations for Food Effect Studies – June 15, 2023"

Learning Objectives

- Understand the importance of assessing the effect of food on drugs
- Comprehend general considerations for designing food effect studies
- Discuss data analysis considerations related to food effect assessment

Scope of the Guidance



- The guidance provides recommendations related to food effect (FE) studies for orally administered drug products under Investigational New Drug applications (INDs) to support new drug applications (NDAs) and supplements to these applications
- Information on fed bioequivalence (BE) studies to be submitted in Abbreviated New Drug Applications (ANDAs) is in the FDA guidance entitled Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021)
- Specific recommendations concerning fed comparability studies are now described in the FDA guidance entitled Bioavailability Studies Submitted in NDAs or INDs — General Considerations (April 2022)

Outline

- Importance of assessing the effect of food on drugs
- Recommendations for food effect (FE) studies
- General considerations for designing FE studies
- Other considerations related to assessing FE
- Summary

Effect of food on safety and efficacy assessment

- Food can increase the systemic exposure of the drug thereby potentially impacting safety and/or efficacy
- Food can decrease the systemic exposure of the drug thereby potentially impacting efficacy
- In some cases, observed increase or decrease in the systemic exposure of a drug when given with food may not be clinically relevant

Some Mechanisms through which Food May Impact Bioavailability

- Increased gastric pH
- Delayed gastric emptying
- Increase in bile salt concentrations
- Others..

Primary Objectives of FE Assessment

- Understand if systemic exposure of a drug is affected by food
- Assess if differences in meal types result in differences in drug exposures
- Provide dosing instructions in the prescribing information in relation to food intake

Recommendations for FE Studies$_1$

- Sponsor should assess the effect of a high-fat meal on the pharmacokinetics of a new drug product *early* in development
  - If a significant change in systemic exposure of the drug is observed, assessing FE with a low-fat meal could be useful

Recommendations for FE Studies$_2$

- Sponsor should consider conducting a pilot study to provide a preliminary assessment of the effect of a high-fat meal on the systemic exposure of the drug
  - Such an assessment can help to determine whether a drug should be administered with food in subsequent trials
- If there are significant differences between the formulation used in the pilot study and the formulation to be used in the pivotal efficacy and safety trials, the sponsor should assess the effect of food on the formulation to be used in the pivotal safety and efficacy trials to determine dosing instructions with respect to food *prior* to conducting the pivotal safety and efficacy trials

Recommendations for FE Studies$_3$

- In cases where the clinical trial formulation is significantly different from the TBM, a relative bioavailability study* and FE assessment using the TBM formulation should be conducted
- In cases where the clinical trial formulation was not significantly impacted by food, and the TBM formulation is not significantly different** from the clinical trial formulation, a FE study with the TBM may not be necessary

** Refer to the FDA guidance entitled Bioavailability Studies Submitted in NDAs or INDs — General Considerations (April 2022)*

*** Refer to FDA guidances entitled SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (October 1997) and 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 (November 1995))*

Recommendations for FE Studies$_4$

- In cases where a biowaiver is accepted to support a formulation change*, a FE study with the TBM formulation might not be necessary
- 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 practical interval of time between drug administration and food

**See the FDA guidance entitled M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021)*

Outline

- Importance of assessing the effect of food on drugs
- Recommendations for FE studies
- General considerations for designing FE studies
- Other considerations related to assessing FE
- Summary

Definitive Studies$_1$

- Trial Design:
  - Randomized, balanced, single-dose, two-treatment (fed and fasted), two-period, crossover design should generally be used
  - A three-way crossover design can be used if the bioavailability* of two formulations is being assessed in the same study

** Refer to the FDA guidance entitled Bioavailability Studies Submitted in NDAs or INDs — General Considerations (April 2022)*

Definitive Studies$_2$

- For drugs with long elimination half-lives (i.e., longer than 24 hours), a single-dose, parallel study design may be more practical
- FE trial should enroll an adequate number of subjects to sufficiently characterize the effect of food on the PK of the drug
  - Sample size depends on the pharmacokinetic variability

* Refer to the FDA guidance entitled *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022)

Types of Meals to Evaluate

- For all orally administered drugs under development, a FE study with a high-fat meal should be conducted
- Sponsor should also consider FE study with a low-fat meal when
  - administration of the oral product with a high-fat meal results in significant increase in toxicity or loss of efficacy
  - administration of the oral product with a high-fat meal in the indicated patient population cannot be tolerated

Test Meals Definitions

		Fat		
Meal Type	Total Kcal	Kcal	Grams	Percent
High-fat	800-1000	500-600	55-65	≥50
Low-fat	400-500	100-125	11-14	25

Subject Selection$_1$

- FE studies are generally conducted in healthy adult subjects
- FE studies may be conducted in patients if
  - safety concerns preclude the enrollment of healthy subjects
  - differential effects of food on the drug are expected in the target patient population because of the underlying disease condition

Subject Selection$_2$

- FE studies should enroll both male and female subjects unless
  - Indication is specific to one sex (for example oral contraceptives)
  - Safety concerns preclude the enrollment of one sex (for example, if the drug is a teratogen, women of childbearing age should be excluded)
- FE studies should enroll subjects with normal hepatic and renal function

Subject Selection$_3$

- FE studies should not enroll subjects who cannot refrain from using concomitant drugs that could confound the results of the FE study. For example
  - drugs that can alter the absorption of other drugs by affecting gastrointestinal motility or by changing the gastric pH
  - drugs that can increase or decrease the metabolism and excretion of the drug for which the FE is being characterized

FE Study Doses

- Definitive FE study should use the clinically recommended dose
- When several doses of a drug that exhibit linear PK will be marketed
  - Use the highest clinically recommended dose
  - If it is unsafe to administer the highest clinically recommended dose to healthy subjects
    - Highest strength of the drug product (instead of the highest dose) can be used in healthy subjects OR
    - FE study can be conducted in patients
- 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

Drug Administration$_1$

- Fasting Conditions
  - Following an overnight fast of at least 10 hours, the drug product should be administered to the 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 until 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

Drug Administration$_2$

- Fed Conditions
  - Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes before administration of the drug product and eat the meal within 30 minutes
  - The drug product should be administered to the 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 until 1 hour after administration of the drug product
  - The study subjects should not consume any food for at least 4 hours after the dose

Drug Administration$_3$

- Modified Fasted Conditions
  - When fasted dosing is necessary because food can significantly increase or decrease the exposure of the drug, the standard, overnight fasted condition might not be practical for patient treatment
    - Results of the overnight, fasted condition might not be applicable to shorter periods of fasting in patients
  - To provide food-drug labeling instructions (e.g., do not consume food within *X hours before* or *Y hours after* drug administration) for such products, FE studies with appropriate separation times between drug administration and food consumption should be conducted
  - Pharmacokinetic data to support pragmatic labeling instructions to prevent food-drug interactions, taking into consideration the frequency of dosing, the patient demographics, the disease condition, and any other relevant factors should be provided

Sample Collection

- For both fasted and fed treatment periods:
  - Samples should be collected in a suitable biological matrix (e.g., plasma) from the study subjects
  - To characterize the complete concentration versus time profile for the drug, the total duration of sampling should cover at least three to five elimination half-lives
  - Different sample collection times for the fasted and fed treatments can be used when co-administration of a drug with food is expected to alter the time course of drug concentrations
  - To determine whether to measure other moieties in addition to the parent drug in the biological matrix, such as active metabolites, sponsors should refer to the FDA guidance entitled *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022)

Outline

- Importance of assessing the effect of food on drugs
- Recommendations for FE studies
- General considerations for designing FE studies
- Other considerations related to assessing FE
- Summary

Waiver of FE Trials

- In most cases, Biopharmaceutics Classification System Class I (BCS Class I) drug products are unaffected by food
  - Some BCS Class I drug products are subject to high first-pass metabolism effects or luminal degradation and can be affected by food
- A FE trial may be waived for BCS Class I drug products that also have a high bioavailability ($F \geq 0.85$)
- The feasibility of obtaining a waiver for a FE trial should be discussed with the Agency

Model-Informed Drug Development Approaches

- In conjunction with FE data in subjects, physiologically based pharmacokinetic (PBPK) analyses can sometimes be used to further assess FE
- PBPK modeling is still evolving, and new applications of PBPK simulation are continuously being evaluated by the FDA
- Sponsors are encouraged to consult the appropriate review division regarding the suitability of the PBPK approach

Drug Products Intended for Administration with Soft Foods

- Labeling of some orally administered drugs (for example oral granules) may include recommendations for use with qualified soft food vehicles (applesauce, pudding etc)
  - Soft food identification and qualification are conducted using in vitro methods (for all soft foods to be included in the label) to demonstrate lack of potential physiochemical interaction between soft food and drug product*
- In vitro assessments do not replace the need for an in vivo evaluation to permit instructions for drug administration with qualified soft food vehicles in labeling
  - For the labeling to indicate that the drug can be sprinkled on soft foods, sponsor should perform additional in vivo, relative bioavailability studies using the soft foods to be listed as vehicles in the proposed labeling

*Refer to the FDA guidance entitled, *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018)

Drug Products Intended for Administration with Liquids as Vehicles

- Labeling of certain oral products (e.g., cyclosporine oral solution) recommends that the product be mixed with a liquid vehicle (e.g., beverage) before administration
  - Qualification of liquids for their use as vehicles should include an assessment and demonstration of lack of a potential interaction between the liquid and the drug product (intact or manipulated), including interactions of the drug substance or excipients with the vehicle
  - For recommendations on in vitro assessments to select appropriate liquid vehicles for drug administration, refer to the FDA draft guidance entitled *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018)
  - Sponsors should contact the FDA to determine what data should be submitted to support proposed labeling instructions regarding the use of specific liquids as qualified vehicles for drug administration

Specific Populations

- Geriatrics (patients aged 65 years and over)
  - Separate FE trial is not recommended
- Pediatrics
  - When a new age-appropriate pediatric formulation is developed, the sponsor should conduct a new FE study with the pediatric formulation in adults. These results can then be applied to the pediatric population
  - Sponsors can use foods and quantities of food that are commonly consumed with drugs in a particular pediatric population
  - The outcomes of FE studies conducted with one soft food vehicle could be extrapolated to other similar soft food vehicles (e.g., same fat, protein, and carbohydrate content) and could support proposed labeling instructions
    - Such extrapolation should be supported by in vitro data which demonstrates a lack of interaction between the drug product (intact or manipulated), including lack of interaction with the drug substance or excipients, with other similar soft food vehicles

Specific Populations

- Pediatrics (continued)
  - Small quantities of liquids or soft foods (e.g., 5-15 mL) used as vehicles for pediatric drug delivery should adhere to the principles described in the FDA draft guidance entitled *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018)
  - When a formulation that is approved for use in adults is approved for use in a pediatric population ≥12 years old, a separate FE study is not necessary
  - A separate FE study might not be necessary if a pediatric formulation is very similar to the adult formulation, and if the pediatric formulation is approved based on a biowaiver approach

Fixed-Combination Drug Products

- Fixed-combination drug products are products with two or more active ingredients combined at a fixed dosage in a single dosage form
- Fixed-combination drug products can exhibit different effects of food compared to when each active drug ingredient is administered alone
  - The effect of food on the various active ingredients of the fixed-combination drug product after administration of the fixed-combination drug product should be assessed
  - FE study might not be necessary if neither drug product when given alone is affected by food, and the sponsor can provide an adequate justification that the fixed-combination drug product would be unaffected by food

Data Analyses$_1$

- Exposure measures and pharmacokinetic parameters (see FE guidance for the detailed list) should be derived from the FE studies and reported
- Individual subject measurements as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation, ranges) should be reported

Data Analyses$_2$

- Exposure measurements (AUC and C_{max}) should be log-transformed before statistical analysis
- 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}
- The clinical relevance of any difference in T_{max} and T_{lag} should also be described

Summary

- FE trials are designed to assess “worst case” scenario; however, it is important to also consider more clinically relevant scenarios
  - Other meal types
  - Modified fasted conditions
- Critical to consider exposure-response relationships when interpreting the results of FE trials
- Providing clear and actionable recommendations in relation to food is important to facilitate the safe and effective use of drugs

Challenge Question #1

Low-fat meal, as defined in the FE guidance, contains how many total Kcal?

A. 400-500

B. 500-600

C. 800-1000

D. 1000-1200

Challenge Question #2

FE Guidance recommends evaluating FE using the following type of meals:

A. High-fat meal only

B. Low-fat meal only

C. High-fat meal and low-fat meal (as needed)

D. None of the above

Questions?