

Background: Food Effect Bioavailability (BA) and Bioequivalence (BE) Studies

(April 10, 2002)

Food induces physiological changes in the gastrointestinal tract (GIT) that can influence the BA of formulations and the BE of two pharmaceutically equivalent dosage forms. A FDA Guidance for Industry on the study design, data analysis and labeling associated with food-effect BA and BE studies was recently posted on the FDA website for public comment. This guidance provides recommendations to sponsors and/or applicants planning to conduct fed BA and BE studies of immediate-release (IR) and modified-release (MR) oral dosage forms.

The Guidance recommends that BA studies are to be conducted by sponsors of New Drug Applications (NDAs) for all new chemical entities and new MR dosage forms to assess how food intake will affect the rate and extent of drug absorption. Based primarily on pharmacokinetic (PK) changes in peak plasma drug levels (C_{max}) and the area-under-the-concentration-time curve (AUC), and the interpretation of these changes using the relationship between PK and pharmacodynamics (PD), the label is intended to explain the optimal way to a drug product relative to meals. It is possible that a drug product may be taken under either fasted condition, with food or without regards to meals. Food-effect BA studies are not the focus of this Advisory Committee meeting discussion.

This Advisory Committee meeting discussion focuses on the topic of food-effect BE studies. Generic oral drug products submitted in Abbreviated New Drug Applications (ANDAs) by sponsors are approved, in part, based on their bioequivalence to a reference listed drug product under fasted conditions, and under fed conditions depending on whether the ANDA product is IR or MR. The food-effect guidance recommends that a BE study under fed conditions be conducted for all MR drug products. For IR products, the decision for a fed BE study is driven by the labeling language of the reference product. When the label of the reference drug product states that it is to be administered under fasted conditions, a fed BE study on the generic drug product is not necessary. A fed BE study is also not necessary when the reference product label does not make any statements about the effect of food on absorption or administration. However, when the reference product label states that there is a food effect or there is no food effect, or that the product may be taken with, or at specific times in relation to, meals, it is necessary that the generic drug product be compared to the reference listed drug product in a fed BE study.

Two important aspects of the food-effect guidance with respect to fed BE studies are the following:

- (1) It provides for a 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 Class 1).

The hypothesis is that the BE of two such dosage forms will not be influenced by food since the drug solubility and dissolution rates of the respective formulations are usually pH- and site-independent and insensitive to differences in dissolution. It is notable that, according to the BCS guidance, it is acceptable to waive fasted in vivo BE studies for BCS Class I drugs/drug products.

(2) It recommends that an equivalence approach be used for fasted versus 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) 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. Study considerations include:

- When food-effect BA and fed BE studies are conducted, it is recommended that a standard two-treatment, two-period, two-sequence crossover design be used with an adequate number of subjects to achieve adequate power for statistical assessment.
- The meals recommended for the fed treatments are the same for both NDAs and ANDAs.

In the case of NDAs, food BA studies may not meet the 90% CI in comparing fasted and fed states and that the effects of food must then be interpreted based upon what is known about the PK-PD relationship for the drug.

Questions for the ACPS Meeting May 7, 2002

1. With regard to waiver of in vivo fed BE studies in ANDAs for BCS Class I drugs/drug products:

- 1.1 To what extent does the committee feel that the literature, in-house and original research data provide sufficient evidence to support the claim that fed BE studies are unnecessary?

1.2. If additional evidence were needed to support the waiver of in vivo fed BE studies for BCS Class I drug/drug products, what form of evidence would be desirable?

2. With regard to using confidence intervals and a criterion to claim bioequivalence between fasted and fed states for new drugs and between fed states for generic drugs (relative to reference products):

- 2.1 To what extent does the committee feel that the issue of food effects can be treated as a lack of equivalence question?
- 2.2 To what extent does the committee feel that a 90% confidence interval with boundaries of 80-125% are appropriate to make a claim of bioequivalence?
- 2.3 What alternative approaches would the committee suggest to demonstrate bioequivalence in the fed state?