



# MYLAN PHARMACEUTICALS INC

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January 25, 2002

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

RE: DRAFT GUIDANCE FOR INDUSTRY ON FOOD-EFFECT  
BIOAVAILABILITY AND FED BIOEQUIVALENCE STUDIES: STUDY DESIGN,  
DATA ANALYSIS, AND LABELING  
[DOCKET NO. 01D-0488]

To Whom It May Concern:

Following are comments pertaining to the above draft guidance dated October 2001.

### General Comments

Before we address our specific point-by-point comments, we have some general concerns about the draft guidance being overly restrictive without compulsory reasons, given that we have had many years of experience in development and marketing of both brand and generic drugs. Specifically, we object to the change of the current criteria (Geometric Mean Ratio) to the 90% confidence intervals (CI) to claim there is no food effect in food-effect BA studies and fed BE studies. We believe this is unnecessary and increases the burden to the pharmaceutical industry.

Food-effect bioavailability (BA) study: New drug applicants are the ones who usually carry out a food-effect BA study. The objective of the study is to perturb the GI environment with a high-fat, high-calorie meal under extreme conditions and to characterize the extent of food effect. This information is then translated to the subject product's labeling to aid dosing regimen and instruction. Therefore, currently there are no pass-fail criteria for the food-effect BA study for new drugs. As long as the extent of food effect is characterized, the drug product is approvable. Pass, fail, or no food effect is not the criteria for drug product approval. The new drug product can claim no food effect but this is not a pre-requisite for drug approval. The current draft guidance only addresses food effect or no food effect by a criterion (90%CI) and does not address the extent of the food effect as information for dosing or the adjustment of dosing.

Fed bioequivalent (BE) study: The current fed BE study is required mainly for approval of generic drug products. Brand-named companies are rarely required to perform a fed BE study for a new drug product (even as a post approval requirement for Components and Composition changes, see SUPAC requirements). And even if a fed BE is required for a brand product, the guidance is not clear on whether the CI criteria would apply. The objective of current fed BE study is to ensure that a reasonable "similarity" between the test and reference formulations is maintained under reasonably fed conditions. Therefore, the extreme condition such as maximum GI perturbation as in the food-effect BA study is not needed. The current fed BE study uses a diet with slightly less fat and calorie contents (the so-called FDA/OGD English Muffin diet). It should be noted that a fasting BE study with very stringent criteria of 90% confidence intervals with appropriate number of subjects is a pre-requisite of generic drug approval. We understand that food can either increase or decrease the variability of the pharmacokinetic parameters. This increase or decrease of variability is extremely difficult to predict and of course will affect the design of the study. Since a very stringent fasting BE study has already been required and the

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fed BE study is essentially a confirmation of similarity, a less stringent criteria can be used as confirmation. This is no different than in the situation that the FDA can waive a BE study by using in-vitro dissolution under certain conditions.

The current criteria for fed BE study is the Geometric Mean Ratio of test and reference formulations not to exceed 20% differences in a fixed number of subjects (N=18). This criterion has been in place for many years. There is no evidence that these less stringent criteria can cause failure of the generic product. On the contrary, generic drug approval using the current criteria, including the fed BE study criterion, has never been questioned. As a matter of fact, two former FDA high level executives (see Notes 1 and 2 at the end), Dr. Roger Williams and Dr. Stuart L. Nightingale, asserted that to date, there are no documented examples of a generic drug product manufactured to meet approved specifications that could not be used interchangeably with the corresponding brand-name drug product. Fed BE is part of those specifications for generic drug approval. This is a very powerful and strong statement. To the best of our knowledge, there is no evidence to date that requires a change of criteria and increase to the burden of the industry. Any changes should be based upon appropriate data. The FDA has found nothing wrong with the current bioequivalence criteria, including fed BE study criterion, and there has not been data provided to support changes in any different study designs.

In the current economic environment, adding regulatory burden without a cause to the industry is not acceptable. Unless the FDA can provide evidence that the current criteria are a danger to public safety, we as responsible scientists and citizens should challenge these unreasonable regulations or requirements.

### **Specific Comments**

The following are our point-by-point (or line-by-line) comments:

Lines 45-49: As explained above, the 80-125% CI should be replaced by the Geometric Mean Ratio within +/- 20%. The extent of food effect on BA study should be reported. This criteria should be used if the sponsor wants to claim no food effect and bioequivalent in the fed BE studies.

Lines 72-73: We suggest the high-calorie and high-fat meal as specified in the Draft guidance be used for both the food-effect BA and fed BE studies.

Lines 101-103: In this sentence, the FDA suggested that for post-approval changes in an approved immediate- or modified-release product that require in vivo redocumentation of BE under fasting conditions, fed BE studies are generally unnecessary. This position (no requirement for a fed BE study) is contrary to the spirit of this Draft guidance (stringent BE criteria) and in agreement with the spirit that the fed BE study is just a confirmation of "similarity" of test and reference drug product (there is no need for a stringent BE criteria). For post-approval changes, including the components and composition changes, a fed BE study is not even needed in the eye of this Draft guidance.

Lines 194-197: The FDA recommended "a sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effect on BA to claim an absence of food effects, or to claim BE in a fed BE study." This statement may be extremely difficult, if not impossible, to carry out in practice. The appropriate number of subjects needed to demonstrate adequate power for a statistical assessment is dependent on the variability of the pharmacokinetic parameters. In order to estimate the number of subjects, some prior information on variability is needed. Food can drastically increase, decrease, or not change the variability of

the pharmacokinetic parameters. This information is normally not available in the literature nor provided in the reference drug labeling. Without that information, the number of subjects with adequate power is usually a guessing game (a waste of resources and not even scientifically reasonable). This is the reason for the current fed BE study - a uniform N=18 - is being used. Again, the objective of the fed BE study is a confirmation of the similarity of the test and reference drug product. With the stringent fasting BE study as the pivotal study, a stringent fed BE study is neither needed nor reasonable. Invariably, 90% confidence interval criteria for fed studies will require larger numbers of subjects to be exposed to test articles. For highly variable products, much larger studies will potentially be required for fed bioequivalence studies. We suggest that the current fed BE study requirements and subject enrollment sample size of 18 be retained.

Lines 201-207: Again, this paragraph allows waiver of food-effect BA and fed BE studies for lower dosage strengths of multiple-strength products, even for modified-release dosage forms, as long as the release mechanisms of the test product are identical and excipients are qualitatively the same for each strength (no requirement on quantitatively the same or proportionality similar). This paragraph further supports the spirit that a stringent criterion is neither needed nor necessary for food-effect BA and fed BE studies.

Lines 211-224: For the sake of consistency, we may want to specify a high-calorie, high-fat meal for both the food-effect BA and fed BE studies to provide maximum GI perturbation.

Lines 335-338: The requirements for performing a BE study when sprinkled on one of the soft-foods mentioned in the labeling is not reasonable. If the test product is BE under fasting conditions and similar under fed conditions, there is no reason to believe that when sprinkled on one of the soft-foods it is not bioequivalent. The same logic can be applied to the situation that if a higher dosage strength is BE, there is no reason to believe that the lower strength is not BE if the release mechanisms are the same and the excipients in the lower strength is qualitatively the same. For the FDA to waive the BE studies for the lower strength but not for the sprinkle BE study is not consistent and not scientifically reasonable. FDA is opening a flood gate for an infinite number of studies for generic approval.

Line 351-355: As described in the previous paragraph, the same applies for special vehicles. FDA is opening a flood gate for an infinite number of studies for generic approval, for example, BE study when co-administered with tea (green tea, red tea, and/or black tea), coffee, milk (0.5%, 1%, 2%, whole, half-and-half), orange juice, cranberry juice, and of course, grapefruit juice and many other juices.

Finally, pharmaceutical regulation is not without risk. Some risks are reasonable and some risks are not reasonable. The food-effect BA study and fed BE study are time-tested and no documented evidence of a significant problem can be found since the 1984 Waxman-Hatch Amendment was passed. The fasting BE study, the food-effect BA study and the fed BE study using normal healthy volunteers (instead of patients) have been accepted and no problems have been identified. Increasing burden to the industry in this without a reason is not acceptable.

Notes:

- (1) In a recent letter from Dr. Roger Williams (FDA) to NAPD regarding the current bioequivalence issues, dated April 16, 1997, he stated "we feel that any change or desire to change FDA's bioequivalence standards should be based upon appropriate data." In his own words, Dr. Williams has indicated that there is nothing wrong with the current bioequivalence criteria and has not seen data to support changes in any different study designs. He also stated that any change should be based upon appropriate data.

[Note: Those statements may not be specifically relevant to food-effect BA study or fed BE study, but they can be applied to BE standards in general and fed BE is part of those standards.]

- (2) In another letter dated January 28, 1998, Dr. Stuart L. Nightingale, Associate Commissioner for Health Affairs at the FDA, declared that there is no public health safety problem associated with the substitution of generic drug (using the current method of bioequivalence). In addition, he asserted that no problems attributed to substitution of one approved drug product for another has occurred (using the current method of bioequivalence). The current draft guidance contradicts those statements and gives an impression that there is something fundamentally wrong with the approval of generic drug products and the criteria of bioequivalence without carefully considering and weighing the cost associated with performing a study with unreasonably stringent criteria.

[Note: Those statements may not be specifically relevant to food-effect BA study or fed BE study, but they can be applied to BE standards in general and fed BE is part of those standards.]

Sincerely,



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Vice President  
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