



January 25, 2002

Docket Management Branch (HFA-305), Docket No. 01D-0488
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD, USA, 20852

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SUBJECT: Comments and suggestions regarding the Draft Fed guidance posted Nov. 28, 2001

Please find enclosed our comments and suggestions regarding the draft guidance for industry entitled "Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling".

We hope that these comments will be helpful to the FDA in the development of the final guidance. Please do not hesitate to contact us if you need any additional information.

Sincerely,

A handwritten signature in black ink that reads "Murray P. Ducharme".

Murray P. Ducharme, PharmD, FCCP, FCP
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The following scientists have participated in the preparation of this document:

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Draft Guidance for Industry
Food-Effect Bioavailability and Fed Bioequivalence Studies:
Study Design, Data Analysis, and Labeling

GENERAL COMMENTS

This guidance incorporates a number of new and innovative ideas for the conduct of BA/BE studies under fed conditions. Since these changes will impact on the results of BA/BE studies, it is worthwhile evaluating carefully the scientific rationale underlying these new concepts. Several comments are included in the following document to put these new ideas into perspective and hopefully improve the proposed guidance.

We understand the FDA's willingness to provide a single Fed Guidance for innovator and generic industry. This ensures that the criteria are objective on both sides and that the minimal requirements are the same. However, the FDA may want to indicate that this guidance contains the minimum requirements. Guidances can be interpreted as guidelines by the industry and may therefore limit scientific research. It will be important to specify that both innovators and generic industries have the flexibility to conduct additional studies. These additional studies may provide a higher level of understanding of the pharmacokinetic and biopharmaceutical properties of the drug substance and drug product under fed conditions.

Please find our comments in the sequence that they appear in the Draft Guidance.

SPECIFIC COMMENTS

Comment #1

II. BACKGROUND

A. Potential Mechanisms of Food Effects on BA (Lines 58-66)

The Draft Guidance states:

"Food, in comparison to fasting conditions, can change the BA of a drug and influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by the following:

- *Delay of gastric emptying*
- *Stimulation of bile flow*
- *Change in gastrointestinal (GI) pH*
- *Increase in splanchnic blood flow*
- *Changes in luminal metabolism of drug substance*
- *Physical or chemical interactions with a dosage form or a drug substance."*

Comment:

The FDA has provided several mechanisms whereby food can alter the BA of a drug. This list is, however, not complete. Other mechanisms can explain food-effect changes in PK. Some are still unknown and others may also include the fact that the plasma becomes more lipidic and may therefore contribute in changing the volume of distribution of a drug and possibly its clearance thereby significantly changing the overall concentration-time profile.

Proposed change:

Instead of writing "*Food can alter BA by the following:*"

We suggest: "Some of the ways Food can Alter BA are the following: "

Comment #2

II. BACKGROUND

A. Potential Mechanisms of Food Effects on BA (Lines 67-68)

The Draft Guidance states:

"Food effects on BA are generally greatest when the drug product is administered immediately after a meal is ingested."

Comment:

The FDA should establish what they mean by immediately after a meal. It remains to be seen if taking a drug in the middle of a meal results in less "food effect" on BA than if a drug is taken immediately after a meal or 15 minutes thereafter.

Proposed change:

The guidance should state that "Food effects on BA should be determined when the drug product is administered shortly after a meal is ingested."

Comment #3:

B. Food Effects on Drug Products (Lines 83 to 84).

The Draft Guidance states:

“However, food can influence BA when there is a high first-pass effect or extensive adsorption, complexation, or instability of the drug substance in the GI tract.”

Comment:

This indicates that an *in vivo* fed study would be needed for Class-I drug such as verapamil.

Comment #4:

III. Recommendations for food-effect BA and fed BE studies

A. Immediate-Release Drug Products

INDs/NDAs (Footnote 2, after line 115).

The Draft Guidance states:

“To test the hypothesis that two rapidly dissolving drug products with a BCS Class I drug substance are unlikely to be bioinequivalent under fed conditions, the FDA is currently conducting clinical research studies at the University of Tennessee. The results of this research will be considered along with literature and in-house data to test this hypothesis as this guidance is being finalized.”

Comment:

The FDA will need to test several drugs to provide a rationale for their position. In addition, the results from the University of Tennessee and other contractors should be made available to the stakeholders for review and comment before the results are applied to future Guidances.

Comment #5:

III. Recommendations for food-effect BA and fed BE studies

A. Immediate-Release Drug Products

1. ANDAs (lines 130-136)

The Draft Guidance states:

“In addition to a BE study under fasting conditions, a BE study under fed conditions is recommended for all orally administered immediate-release drug products, with the following

exceptions:

When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) as defined in the BCS guidance, or”

Comment:

If a waiver is granted for IR formulations of BCS Class 1 drugs, we are not sure if scientific evidence is available to ensure that it is not possible to make a non-BE formulation of an IR class I drugs that otherwise meets the FDA criteria for a waiver. Have you considered the possibility that “inactive” ingredients may influence the activity of carrier efflux proteins like P-Glycoprotein and therefore may influence the comparative absorption of two formulations of the same “active” ingredient?

Comment #6

IV. Study Considerations

E. Administration – Fed Treatments (lines 236-237)

The Draft Guidance states:

“The meal should be consumed over 30 minutes with administration of the drug product immediately after the meal.”

Comment:

It is difficult to coordinate meal consumption and administration of the drug product the way it is currently stated in the guidance.

Proposed change:

The meal should be started 30 minutes prior to the administration of the drug product. Volunteers/patients should be told to make every effort to eat their meal between 20 and 30 minutes, so that the drug could be taken almost immediately after the meal.

Comment #7

V. Data analysis and labeling (lines 259-268)

The Draft Guidance states:

“The following exposure measures for assessment of BA and BE should be obtained from the

resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

Total exposure, or area under the concentration-time curve (AUC_{0-inf}, AUC_{0-t})

Peak exposure (C_{max})

Time to peak exposure (T_{max})

Lag-time (t_{lag}) for modified-release products, if present

Terminal elimination half-life

Other relevant pharmacokinetic parameters”

Comment:

Although we believe that the data analysis and labeling issues should be addressed only after the rationale and study design issues have been finalized (e.g., are we going to analyze the data with compartmental PK (T_{lag}) or with noncompartmental PK (C_{max} and AUC)) we do have some general suggestions on the data analysis and labeling section.

The purpose of a BE study is to compare two formulations in terms of their rate and extent of bioavailability. In pharmacokinetics, these processes are described by the parameters K_a (absorption rate constant) and F (bioavailability). Since individual pharmacokinetic analysis using individual compartmental methods is very susceptible to noise in a data set, pharmacokineticists have used the noncompartmental approach to estimate AUC_{0-inf} (extent of bioavailability) and the C_{max} (rate and extent of bioavailability) parameter values. In most cases, noncompartmental methods are both robust and simple. If an investigator desires to further evaluate the PK properties of a drug substance or drug product, appropriate compartmental PK analyses could provide additional useful parameter values such as lag time, absorption rate constant, relative bioavailability, etc... This guidance should recommend to present the following robustly calculated noncompartmental PK parameters:

C_{max}

T_{max}

AUC_{0-t}

AUC_{0-inf}

K_{el}

Approval criteria parameters should only include C_{max} and AUC_{0-inf}. Although AUC_{0-t} should not be used as an approval criterion, it is important to determine what fraction of AUC_{0-inf} is actually measured during the sampled interval. Therefore, instead of asking to pass on AUC_{0-t}, we believe that the agency should concentrate on making sure that the PK of a drug was correctly assessed by enforcing that the extrapolated AUC should be less than 10% on average.

Comment #8

V. Data analysis and labeling (lines 270-275)

The Draft Guidance states:

"The 90% CI should be provided for AUC_{0-inf}, ... and C_{max}."

Comment:

It is a sound scientific decision to ask to pass on confidence intervals for fed studies for AUC_{inf} and C_{max}.

Comment #9

V. Data analysis and labeling (lines 270-275)

The Draft Guidance states:

"The 90% CI should be provided for ..., AUC_{0-t} and ..."

Comment:

The 90% CI can be provided for AUC_{0-t} for information purposes but should not be a criteria for bioequivalence. In certain circumstances, the AUC_{0-t} will not be a correct measure of the extent of bioavailability. For example, if concentrations at the end of a sampling interval are close to the limit of detection, one may end up comparing in the same subject between formulations an AUC₀₋₂₄ with an AUC₀₋₃₆. This means that two drug formulations may not meet the bioequivalence criteria on AUC_{0-t} (because we are comparing AUC₀₋₂₄ with AUC₀₋₃₆ in certain subjects) when they are in fact truly bioequivalent (e.g., passing on AUC_{inf}, C_{max}, AUC₀₋₂₄, AUC₀₋₃₆, etc...).

Comment #10

V. Data analysis and labeling (lines 284)

The Draft Guidance states:

*"For an NDA, a food effect on BA is **indicated** if the 90% CI for the ratio of population geometric means...."*

Proposed change in wording:

For an NDA, a food effect on BA is **demonstrated** if the 90% CI for the ratio of population geometric means....

Comment #11

V. Data analysis and labeling (lines 286 and 305)

The Draft Guidance states:

“AUC0-inf (AUC0-t) or Cmax...”

Comment:

Please clarify why AUC0-t is written under parenthesis.

Comment #12

V. Data analysis and labeling (lines 317 to 318)

The Draft Guidance states:

“Although no criterion applies to Tmax, the Tmax values for the test and reference products are expected to be comparable based on clinical relevance.”

Comment:

We agree with the FDA that the Tmax should not be a criterion for BE using the noncompartmental pharmacokinetic approach. A reason for this could be a lag-time in the absorption of the drug. A lag time can be seen with any type of oral formulation, and is not restricted to modified release formulations. Drugs associated with an absorption lag-time, will be frequently associated with a different Tmax in the same individual with the same drug formulation. Only compartmental pharmacokinetic analyses can provide robust information on the lag time of a drug-formulation and on their specific absorption rate constant.

Therefore, Tmax comparisons can lead to misinterpretation.

Proposed change:

“Tmax values should be provided for all formulations.”

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