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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



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January 24, 2002

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

Re: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and labeling [Docket No. 01D-0488; 66 *Federal Register* 59433, November 28, 2001]

Dear Sir/Madam:

The Pharmaceutical research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than \$30 billion in 2001 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

Food-effect bioavailability/bioequivalence studies are an important part of the clinical development program for new medicines. PhRMA, therefore, appreciates the opportunity to provide the attached comments on the Draft Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling.

We hope that you will give careful consideration to the attached comments as you work to finalize the guidance. Please contact me if there are any questions.

Sincerely,

Alice E. Till, Ph.D.

Att.

01D-0488

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Pharmaceutical Research and Manufacturers of America

Comments on "Draft Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling [Docket No. 01D-0488; 66 Federal Register 59433, November 28, 2001]"

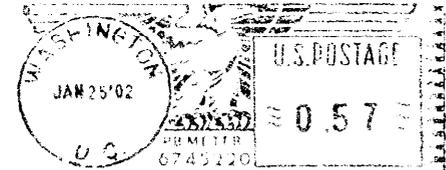
Section	Page # and Line #	Original Text	Comment
General			<ol style="list-style-type: none"> 1. The rationale of combining two topics, food-effect BA and fed BE, in one document is unclear and potentially creates unnecessary confusion. 2. It would be useful to add definitions of "Food Effect BA" and "Fed BE" up front before getting into the detail of the guidance.
I. Introduction	p.2, lines 45 - 49	<p>"It recommends that an equivalence approach be used for, 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....."</p>	<ol style="list-style-type: none"> 1. Can a sponsor apply different approaches, e.g., the population BE (PBE) or the individual BE (IBE), for highly variable drugs? 2. It is unclear why a equivalence limit of 80-125% should be the cutoff for determining the significance of a food effect. In particular, experience has shown that the limit is too stringent for C_{max} in a fast vs. fed comparison.
III. A. 1. INDs/NDAs	p.3, lines 109 - 115	<p>"Food-effect BA or fed BE studies ... to guide dosage form development, ... This guidance recommends that food-effect BA and fed BE studies be conducted early in the drug development process using the formulation to be employed in the clinical trials ..."</p>	<ol style="list-style-type: none"> 1. Recommend to delete "or fed BE" from the sentence. We do not see the rationale for bioequivalence during fed conditions between early formulations. 2. On lines 113-115 is a statement that the food effect and fed BE studies should be conducted "early in the drug development process" with the formulation intended for the pivotal studies. In lines 109-110, it is suggested that the food effect study is useful to "guide dosage form development." These could be interpreted as contradictory. 3. Clarification regarding whether the dosage form to be used in the food effect study should match that in the pivotal clinical trial is needed.
III. A. 1. INDs/NDAs	p.4, line 124 - 126	<p>"When the fasting study does not establish BE, and food</p>	<p>It is not entirely clear what is the implication of this sentence. If BE</p>

		significantly affects the drug product's performance in vivo (BA), it is important to determine food effects on the to-be-marketed formulation."	was not established in the fasting state, but <u>was</u> in the fed state, and the labeling was to recommend dosing in the fed state, the FDA would accept a bioequivalence claim?
III. A. 2. ANDAs	p.4, lines 130 - 142	"In addition to a BE study ... BE study under fed conditions is recommended ... , with the following exceptions: · ... · When the label of the RLD does not make any statements about the effect of food on absorption or administration.	Since food effects may well be formulation specific, the bio-availability of the new product may be different, compared to the RLD, during fed conditions. We therefore consider it a potential danger for the patient when switching to a new product, if that product has not been studied during fed conditions.
IV. A. General Design	p.5, line 176	"A randomized, balanced, single-dose, two-treatment (fed vs. fasting), ... is recommended for studying the effects of food..."	Since most drugs are administered repeatedly, multiple-dose food effect studies would be more relevant in a clinical setting than single-dose studies.
IV. A. General Design	p.5, lines 184 - 185	"A sponsor can propose alternative study designs, but the scientific rationale and justification for these study designs should be provided in the study protocol."	Is the agency suggesting the food effect and fed BE strategies be discussed prior to study conduct?
IV. B. Subject Selection	p.5, lines 194 - 197	"A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment Typically, a minimum of 12 subjects should complete the food-effect BA and fed BE studies."	What is the rationale for proposing a minimum of 12 subjects? Shouldn't the sample size be determined by an adequate power as suggested in the first sentence? Recommend to delete the sentence after "Typically".
IV. C. Dosage Strength	p.6, line 201	"In general, the highest strength of a drug product should be tested in all food-effect BA and fed BE studies."	<ol style="list-style-type: none"> 1. Is the intent that the food effect be evaluated at the highest strength ever tested in clinical trials or at the highest strength to be marketed? 2. As these programs advance or with line extensions, higher dose strengths may be selected after the food-effect evaluation is performed. Is the agency recommending that the Food-BA effect evaluation needs to be repeated? 3. In the case where prior results from the food effect study with a lower strength are available, the results of these studies should be

			<p>considered</p> <p>4. The following revision is suggested in order to avoid confusion: "In general, the highest strength of a drug product (not necessarily the highest dose) should be tested in all food-effect BA and fed BE studies."</p>
IV. E. Administration	p.6, lines 236-237	"The meal should be consumed over 30 minutes with administration of the drug product immediately after the meal."	Should a volunteer be excluded in the trial if the meal is not completely consumed?
IV. E. Administration	p.6, lines 237 - 238	"The drug product should be administered with 240 ml (8 fluid ounces) of water."	The total volume of fluid intake, 16 fluid ounces within an hour, might be too excessive for volunteers in the fed arm. Will this difference in total fluid volumes between treatments confound with the food effect to be tested?
IV. F. Sample Collection	p.7, line 252	"so that fasting and fed studies can have different sample collection times."	Add "BE" to the sentence : "so that fasting and fed BE studies can have different sample collection times." will improve the clarity.
V. Data Analysis and Labeling	p.7, line 263	"Total exposure, or area under the concentration-time curve (AUC ₀₋₄ , AUC _{0-t})"	The first term shown in parentheses is ambiguous; on the screen this appears as AUC _{0.} and in the printed version of the PDF, this is displayed as AUC _{0.4} . Please clarify what this parameter is intended to be (and if AUC _{0.4} is intended please provide the rationale). AUC _{0-t} needs to be defined here (although it is well defined in other guidance documents).
V. Data Analysis and Labeling	p.7, line 268	"Other relevant pharmacokinetic parameters"	Can it be more specific on what "other" PK parameters should be considered?
V. Data Analysis and Labeling	p.7, line 270	"Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported."	Which group averages to be used, arithmetic mean or geometric mean? If it is the latter, what definition should be used for SD and CV?
V. Data Analysis and Labeling	p.7, lines 271 - 275	"Log-transformation of exposure measurements prior to analysis is recommended. The 90% CI should be provided for AUC _{0.} , AUC _{0-t} and C _{max} ..."	<p>1. To be consistent with the rest of the document it should read, "The 90% CI for the ratio of population geometric means (between test and reference) should be"</p> <p>2. More guidelines of how to</p>

			<p>analyze T_{max} and half-life should be given here, e.g., should T_{max} be log-transformed or other nonparametric methods may be considered?</p> <p>3. It is not sufficient to calculate summary statistics for T_{max} in each arm and then compare since this ignores the nature of the crossover design.</p>
V. Data Analysis and Labeling	p.8, line 286 and line 305	“the equivalence limits of 80%-125% for either AUC_{0-t} (AUC _{0-t}) or C_{max} .” and “the equivalence limits of 80%-125% for AUC_{0-4} (AUC _{0-t}) and C_{max} .”	These are inconsistent statements. Should all AUC_{0-t} , AUC_{0-t} and C_{max} meet the equivalence criteria or a subset? How about AUC_{0-inf} ?
V. Data Analysis and Labeling	p.8, lines 287 - 288	“...or when a food-effect BA study indicates a large food effect (defined as > 20% higher ...),”	<p>1. It seems to be redundantly defined. Technically it is highly unlikely for there to be a 20% or greater change and still have a 90% CI contained inside 80-125%.</p> <p>2. What is the impact on labeling if Food-BA effect is statistically important (i.e., outside the 90% confidence interval) but regarded as clinically unimportant?</p>
V. Data Analysis and Labeling	p.8, lines 305 - 307	“In this case, ... of the label that no food effect on BA is expected provided that the T_{max} values are also similar between the fasted and fed treatments.”	It is unclear why the equivalence of T_{max} is clinically important for justifying no food effect. It is not uncommon that food affects the time where peak exposure occurs without significantly changing C_{max} and AUC. In particular, T_{max} is usually delayed with a high-fat meal.

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