



HFA-325

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 31 2003

James H. Schafer, D.V.M.
800 Helena Court
Fort Collins, Colorado 80524

Re: Docket No. #02P-0489

Dear Dr. Schafer:

This is the final response from the Food and Drug Administration (FDA) to your Citizen Petition filed November 15, 2002 (Docket #02P-0489). FDA issued an interim response to the petition on May 15, 2003. This is the final response to your Citizen Petition #02P-0489, which requests that the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA, agency) revise its bioequivalence guidelines.

Specifically, your citizen petition requests that CVM revise its 1996 *Bioequivalence Guidance* (and its subsequent versions dated July 2000, October 2000, and October 2002) so that it is harmonized with the European Union's (EU) guidance, *Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products* (effective July 11, 2001). The petition focuses on the 90% confidence interval limits for the pivotal bioequivalence parameters, area under the concentration versus time curve (AUC) and observed peak drug concentrations (C_{max}). CVM's *Bioequivalence Guidance* currently states that the confidence interval for untransformed data should be 80-120%. CVM is asked to specifically allow for consideration of bioequivalence for a generic product if the 90% confidence intervals about the mean calculated for C_{max} are within the limits of 70% to 130% for untransformed data in situations with complex absorption kinetics, situations where the reference product has a highly variable C_{max} or where, based on clinical evidence, C_{max} has little therapeutic or toxic implication. For the reasons described below, your petition is denied.

Under the Generic Animal Drug Patent Term Restoration Act (GADPTRA),^[1] an application for a generic animal drug must show that the product has the same active ingredients as the approved animal drug product and, with limited exceptions, that it is bioequivalent to the approved animal drug product. Ensuring this interchangeability for all products approved as abbreviated new animal drug applications (ANADAs) is the goal of the agency's generic drug review process. Since there can ultimately be several marketed generic versions of a single pioneer product, the bioequivalence criteria (comparing the generic to the pioneer product) need to ensure that therapeutically identical responses will be achieved, regardless of whether the innovator product is exchanged for a generic formulation or whether one generic formulation is being switched to another. However, FDA believes that if it adopts the EU guidelines' very wide confidence limits, the agency would no longer be assured of product interchangeability.

The use of blood level data to support product bioequivalence is contingent upon the assumption that if two products result in superimposable serum drug concentrations, they will perform in an identical manner. In other words, so long as the active moiety of two formulations is identical, the excipients included in each formulation are clinically inert, and the two products produce indistinguishable systemic patterns of exposure to the active ingredient(s), we assume that the body cannot distinguish

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between the sources of an active agent. (Of course, this assumption is inappropriate for those products whose actions do not require transport to the site of action via the blood.) Thus, statistics have been developed as a tool with which to judge the degree of superimposition of the test product and reference product blood level profiles. As we deviate from this assurance, we also increase the risk of having two products that fail to perform in a comparable manner.

In your petition, you express concern regarding CVM's strict application of the 80-120% confidence limit criteria for assessing product comparability based upon C_{max} . From a pharmacokinetic perspective, we agree that C_{max} is not a pure measure of absorption rate, but rather reflects both rate and extent of absorption (Steinijans, *et. al.*, 1992; Bois, *et. al.*, 1994). In addition, peak concentrations will also be affected by drug-specific attributes such as the rate and extent of intercompartmental exchange as well as the rate of drug elimination. Therefore, variability attributable to each of these sources impacts the true C_{max} value. Compounding this problem is that C_{max} , as defined by model-independent methods, is highly dependent upon drug sampling time. Nevertheless, in the majority of situations, FDA continues to consider C_{max} a highly informative metric upon which to compare the *in vivo* performance characteristics of a dosage form. We believe that assurance of superimposition of the blood level profiles is an important consideration when evaluating product bioequivalence. And at present, we consider the combined assessment of AUC and C_{max} to provide an optimal method for assessing the relative shapes of the blood level profiles associated with the test and reference products.^[2]

We do agree, however, that one of the fundamental problems associated with the use of C_{max} is that it tends to exhibit greater variability than does AUC. The EU's guidelines state that, as a general rule, the difference between mean AUC and C_{max} values should be contained within the limits of 80 to 120%. However, since C_{max} may exhibit a high degree of variability and is strongly dependent on the sampling scheme, the guidelines would consider it appropriate to expand the confidence limits to 70 to 130% based upon clinical evidence. FDA has concerns with adopting the EU guideline's expanded confidence limits because it would not provide assurance of product interchangeability. This can be particularly problematic if multiple generic versions of a single pioneer are available.

To demonstrate a consequence of the 70 to 130% interval, we examined the extremes in drug bioavailability that could exist between generic products approved under this interval versus the 80 to 120% interval. Using intrasubject variability estimates that have been observed with veterinary products, we developed sample data for the following four situations:

- (1) An approvable product for which the upper confidence bound was at the 1.20 upper limit. This product is termed EX A1.
- (2) An approvable product for which the lower confidence bound was at the 0.80 lower limit. This product is termed EX A2.
- (3) An approvable product for which the upper confidence bound was at the 1.30 upper limit. This product is termed EX B1.
- (4) An approvable product for which the lower confidence bound was at the 0.70 lower limit. This product is termed EX B2.

We assumed that within each dataset, the parameter was normally distributed (allowing for the estimation of the confidence limits about the difference in treatment means to be based upon the use

of untransformed data), and that the bioequivalence trial was conducted as a crossover study employing 24 subjects. The reference product conditions remained constant throughout for each of the scenarios. Table 1 provides the means, coefficients of variation, and confidence bounds associated with each of these examples.

Table 1: Sample data to demonstrate consequences of difference between the 70-130% and 80-120% bioequivalence criteria.

	Mean test	Mean ref	%CV test	% CV ref	N	Lower Bound	Upper Bound
Ex A1	109.6	100	20	20	24	0.992	1.200
Ex A2	91	100	25	20	24	0.803	1.017
Ex B1	119.1	100	20	20	24	1.082	1.300
Ex B2	80	100	25	20	24	0.700	0.900

To determine the impact of these differences in bioequivalence criteria, we compared the confidence limits associated with products that can be declared bioequivalent under each of them (Figure 1). We find that although the confidence limits overlap for the two sets of products under the 80-120% interval, the confidence limits do not overlap for the products approved under the 70-130% interval. Through this example, we find that there is a greater chance of having generic products that are therapeutically distinguishable when employing the wider criteria allowed, in certain circumstances, under the EU's guidelines. Therefore, we decline to adopt this criteria at this time.

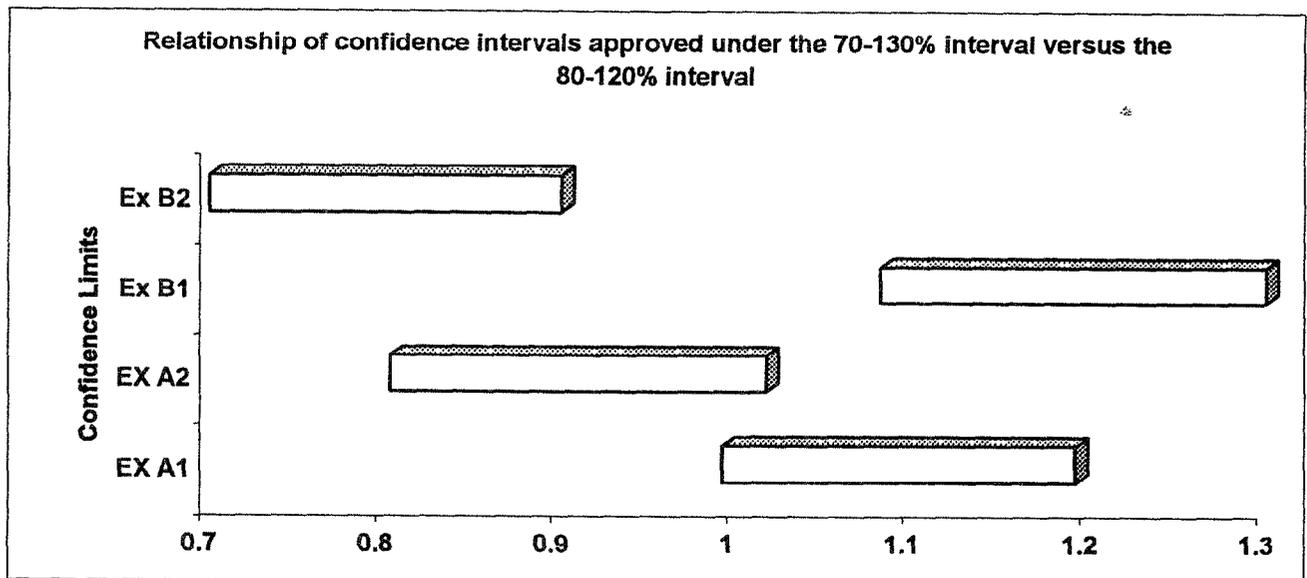


Figure 1: Use of confidence intervals to demonstrate the impact of expanding the confidence limits from 80 – 120% to 70-130%.

On the other hand, FDA does recognize that there are circumstances where a pioneer product could fail to demonstrate bioequivalence even if tested against itself. In this regard, failure to meet *in vivo* bioequivalence criteria can be attributable to the magnitude of the differences between treatment means or to the variability associated with the blood level parameters. Clearly, large differences between treatment means or a more variable test than reference formulation could seriously impair product switchability. However, if a high level of variability is observed with both products, or if the test product has substantially less variability than does the reference, average bioequivalence methods (as described in CVM's *Bioequivalence Guidance*) could fail to adequately identify products that will, on the average, produce comparable therapeutic effects.

As noted in your petition, this point was recognized by FDA's Center for Drug Evaluation and Research and has provided the basis for the development of alternative metrics. In their guidance entitled *Statistical Approaches to Establishing Bioequivalence (January, 2001)*, they provide three methods for estimating product bioequivalence: average, individual, and population bioequivalence. While the criteria for average bioequivalence is held constant at +/-20% (untransformed data) or -20, +25% (Ln-transformed data), the confidence bounds for the population and individual bioequivalence approaches are scaled to the observed variability in the dataset. If the test product is more variable than the reference product, the acceptable difference between the treatment means is reduced. Conversely, if the reference product is more variable than the test product, greater leeway between treatment means may be permissible.

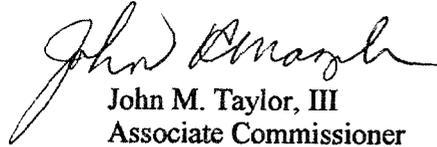
The individual bioequivalence approach ensures product switchability but requires the use of an extended crossover design. FDA will consider the use of this statistical method for animal drugs if proposed during the protocol development phase of the product application. However, FDA recognizes that such designs may be problematic in studies employing rapidly growing animals, smaller sized species with inherent limitations on the number of blood samples that can be safely collected from each individual, when using species subject to stress responses, or when testing products associated with long terminal elimination half-lives (due to either prolonged elimination or absorption processes).

The population bioequivalence approach, as stated in the CDER guidance, can theoretically be applied to parallel design studies. Nevertheless, despite its theoretical applicability, extensive additional effort will be needed before the population bioequivalence algorithm can be applied to parallel studies.

Given the state of our current scientific framework, including the aforementioned limitations for animal drugs, FDA continues to work within the domain of average bioequivalence concepts and the bioequivalence criteria of 80 to 125% (based on Ln-transformed data and the two-one-sided test procedure as described in the current CVM *Bioequivalence Guidance*). But we agree that additional work is needed to develop metrics applicable to those situations when the reference product would be unable to be demonstrated as bioequivalent to itself. Accordingly, FDA will explore alternative approaches to accommodating the evaluation of highly variable drugs as time and resources permit. In addition, FDA welcomes suggestions for alternative statistical approaches for assessing product

bioequivalence for specific animal drug products, preferably during protocol development and prior to conducting the pivotal bioequivalence study.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "John M. Taylor, III".

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

cc: HFA-305 (Docket #93P-0337)

References:

Barrett JS, Batra V, Chow A, Cook J, Gould AL, Heller AH, Lo MW, Patterson SD, Smith BP, Stritar JA, Vega JM, and Zariffa N (2002). PhRMA perspective on population and individual bioequivalence. *J. Clin. Pharmacol.*, 200, 30: 561 – 570.

Bois FY, Tozer TN, Hauck WW, Chen ML, Patnaik R, Williams RL. (1994) Bioequivalence: performance of several measures of extent of absorption. *Pharmaceutical Research*, 11, 715-722.

Steinijans, V.W., Hauschke, D., and Jonkman, J.H.G. (1992) Controversies in bioequivalence studies. *Clinical Pharmacokinetics*, 22, 247-253.

^[1] Generic Animal Drug and Patent Term Restoration Act (GADPTRA), Pub. L. 100-670, Nov. 16, 1988, 102 Stat. 3971, amends the Federal Food, Drug, and Cosmetic Act with regard to generic animal drug products and bioequivalence.

^[2] In fact, for most oral dosage forms, FDA's Center for Drug Evaluation and Research (CDER) continues to regard C_{max} as a metric for estimating similarity of product peak exposure. In this regard, CDER's recent guidance entitled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations* states the following:

Both direct (e.g., rate constant, rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residence time, C_{max} normalized to AUC) pharmacokinetic measures are limited in their ability to assess rate of absorption. This guidance, therefore, recommends a change in focus from these direct or indirect measures of absorption rate to measures of systemic exposure. C_{max} and AUC can continue to be used as measures for product quality BA and BE, but more in terms of their capacity to assess exposure than their capacity to reflect rate and extent of absorption.