Suitability of Various Noninfinity Area Under the Plasma Concentration–Time Curve (AUC) Estimates for Use in Bioequivalence Determinations: Relationship to AUC from Zero to Time Infinity (AUC0–INF)

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The influence of random error and elimination rate on estimates of the area under the curve from zero to time infinity (AUC0–INF) was determined in a simulation study using noninfinity measured AUC values (i.e., AUCTM, area to a measured common sampling time, and AUC0–LAST, area to the last measured sampling time). Further, the extent of absorption of generic danazol, baclofen, and oxazepam was determined using measured methods of estimating area under the curve in bioequivalence studies. The noninfinity AUC estimates and their 90% confidence intervals for the difference in product means were compared for each individual drug. Products chosen fulfilled one of the following three criteria: (1) a high "apparent intrasubject variability" and a half-life greater than 8 hr (danazol); (2) a low apparent intrasubject variability and a half-life less than 4 hr (baclofen); and (3) products exhibiting a low apparent intrasubject variability and a half-life greater than 8 hr (oxazepam). For the simulated data, AUCTM performed best when subjects had similar half-lives (i.e., low variability), which results in AUCTM = AUC0–LAST. On the other hand, AUC0–LAST worked best with a high fractional standard deviation (fsd) and a short elimination half-life (i.e., less than 4 hr). The noninfinity 90% confidence intervals for danazol and oxazepam were inconsistent with those observed at AUC0–INF. However, baclofen, which has a short elimination half-life, exhibited good agreement between the noninfinity and the AUC0–INF 90% confidence intervals. However, across all three drug groups, the comparison based upon the area calculated from time zero to the last quantifiable concentration, AUC0–LAST, consistently provided the best approximation of AUC0–INF.

KEY WORDS: area under the plasma concentration–time curve (AUC); bioavailability; noninfinity AUC estimates; 90% confidence intervals; danazol; baclofen; oxazepam.

INTRODUCTION

Interproduct bioequivalence comparisons involving the extent of drug absorption are commonly based upon the area under the plasma concentration–time curve (AUC) extrapolated to time infinity (AUC0–INF) (1). However, because of inadequate assay sensitivity and fluctuating drug concentrations, AUC0–INF is difficult to determine and noninfinity AUC estimates are frequently employed (e.g., Refs. 2–9).

Noninfinity AUC estimates have been defined in a variety of ways. For example, AUC may be determined from time zero to the last quantifiable plasma drug concentration (AUC0–LAST). In this case, the number of plasma concentrations included in the estimate can vary both within and between study subjects (2). Alternatively, AUC may be limited to some common time when all subjects exhibit demonstrable plasma drug concentrations (3,4). This method can result in substantial truncation of the available blood-level data.

The appropriateness of using various noninfinity AUC estimates as an index of the extent of drug absorption has been well described (10,11). However, although the error associated with estimates of noninfinity AUCs is critical to the interpretation of bioequivalence data, the variability associated with these parameters has not been rigorously addressed. Therefore, we examined the effect of varying the "definition" of the noninfinity AUC estimates both on the resulting interproduct bioavailability comparisons and on the statistical confidence associated with these comparisons. These noninfinity estimates are further evaluated for their consistency with the 90% confidence intervals (two one-sided t tests) for the interproduct difference observed when the data are extrapolated to time infinity.

To ensure that our conclusions are not biased by the bioavailability characteristics of a specific drug, these relationships are explored under the following conditions.

Simulated Data

(1) High fsd
   (a) Terminal drug elimination half-life less than 4 hr
   (b) Terminal drug elimination half-life exceeding 8 hr
(2) Low fsd
   (a) Terminal drug elimination half-life less than 4 hr
   (b) Terminal drug elimination half-life exceeding 8 hr

Experimental Data

(1) Products exhibiting low "intrasubject variability" and long terminal elimination half-lives (greater than 8 hr)
(2) Products exhibiting high intrasubject variability and short terminal elimination half-lives (less than 4 hr)
(3) Products exhibiting low "apparent intrasubject variability" and long terminal elimination half-lives (greater than 8 hr)

MATERIALS AND METHODS

Bioequivalence Study Protocols

Acceptability of volunteers was based on their medical histories, physical examination, and laboratory tests. There was a 1-week washout period between study phases for baclofen and danazol and a 2-week washout for oxazepam. Study details for each are presented in Table I.

Data Simulation

Plasma concentration–time data for a linear one-compartment body model with elimination from the central

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Table I. Study Characteristics for the Danazol, Baclofen, and Oxazepam Bioequivalence Studies

	Danazol[a]	Baclofen[a]	Oxazepam[b]
Subjects	35 surgically sterile females	29 males	28 males
Dose	2 × 200-mg capsules	1 × 20-mg tablet	1 × 30-mg tablet
Sampling times	0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 84 hr	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hr	0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 60 hr
Reference drug	Danocrine, Winthrop-Breon	Lioresal, Ciba-Geigy	Serax, Wyeth
Assay CV	14%–4 ng/ml[13–14]	12%–60 ng/ml[15]	2.1%–25 ng/ml[16]
Linearity	1–150 ng/ml	20–500 ng/ml	10–750 ng/ml

[a] Two-treatment, two-period crossover.
[b] Three-treatment, three-period crossover.

compartment was generated using CONSAM (12). The parameters used in the simulations were k_a Test = 0.8 hr^{-1} [K_e = 0.3 hr^{-1} and K_e = 0.08 hr^{-1} with an fsd (fractional standard deviation) = 10 and 20% for both values of K_e] and k_a Reference = 0.4 hr^{-1} (K_e and fsd values used were identical to those of Test data sets). The volume of the central compartment was 10 liters.

Concentration–time data were generated at 0, 0.25, 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5, 9.5, 10.5, 20.5, 30.5, 40.5, 50.5, 60.5, 70.5, and 80.5 hr following oral administration of 100 mg of drug (F = 1).

Data Analysis

AUC was estimated using the linear trapezoidal method. For each drug product and simulated data set, the plasma concentration time curves for the AUC estimates were defined as follows.

1. Calculations involving only *measured* drug concentrations
   a. AUC0–LAST: AUC calculated to the last quantifiable plasma concentration for each subject within each treatment. All subjects are included in the analysis.
   b. AUCTM: AUC calculated at time TM, which represents a common time at which there is a quantifiable blood level for each subject. This classification of measured levels results in some plasma levels for subjects with longer half-lives being deleted and includes only subjects that receive *both* treatments.
2. Calculation of *extrapolated* concentrations: AUC0–INF = AUC0–LAST plus the area from time T to infinity (1). In this case, extrapolation is obtained in accordance with the expression

$$C_t/K_e$$

where C_t is the last quantifiable drug concentration and K_e is the first-order elimination rate constant.

For the oxazepam data set, absorption rate constants, k_a, were determined for the test and reference products using Estrip (17). The appropriate number of exponentials was assessed using the Akaike information criterion (18).

Statistical Analysis

An analysis of variance (ANOVA) was performed on all data sets (19). The model contained main effects of subjects, period, and treatment. Sequence was analyzed as a between-subject variable. The confidence interval about the difference between the test and reference means, expressed as a percentage of the reference mean, was determined (20). The 90% confidence intervals were determined on the basis of the least square means, the estimated difference between these means, and the error associated with the least-squares estimate (residual error of the ANOVA). The mean square error from the ANOVA, whose estimate is based upon the difference between test and reference AUC values for each subject, was used as a measure of apparent intrasubject variation. By taking the within-subject differences, the subject effect is removed from the statistical model, resulting in the intersubject component of variance being removed from the calculations.

A profile analysis (21) was conducted on the oxazepam data set to evaluate the statistical significance of the observed changes in the magnitude of the difference between test and reference AUC values over time.

RESULTS

Simulated Data

The results of the simulation study are presented in Table II. The 90% confidence intervals for measured AUC values and for AUC0–INF, expressed as a percentage of the reference mean, indicated that AUCTM provided a reasonable estimate of AUC0–INF only when its confidence interval was the same as that for AUC0–LAST. This occurred at the half-life of 8.6 hr at 10% fsd. Otherwise, the AUCTM confidence interval grossly overestimated the infinity confidence interval. As for AUC0–LAST, it appeared to provide the best estimate of AUC0–INF confidence intervals when the elimination half-life was short (i.e., 2.3 hr). This result

Table II. The 90% Confidence Intervals and the Test/Reference Mean Ratio Resulting from 10 and 20% Fractional Standard Deviation Added to the Simulated Data

	AUC(TM)	*T/R*	AUC0–Last	*T/R*	AUC0–INF	*T/R*
10% fsd, $t_{1/2}$ = 8.66 hr	103.2–107.5	1.05	103.5–107.5	1.05	99.1–104.4	1.01
10% fsd, $t_{1/2}$ = 2.3 hr	113.6–117.6	1.15	101.3–105.2	1.03	98.1–104.5	1.01
20% fsd, $t_{1/2}$ = 8.66 hr	108.9–116.1	1.12	91.8–103.3	0.90	90.3–101.8	0.96
20% fsd, $t_{1/2}$ = 2.3 hr	110.1–119.0	1.14	91.5–100.7	0.96	91.1–101.7	0.96

did not appear to be measurably influenced by a random error of up to 20%.

Experimental Data

Danazol

Rate of Absorption. The mean pharmacokinetic parameters and the associated variability estimates for danazol are summarized in Table III. The two products show comparable maximum concentration (C_{max}) and time to maximum concentration (T_{max}). However, mean C_{max} and T_{max} values exhibited a large fsd for the test product due to several subjects having large C_{max} values resulting from an apparent rapid rate of drug absorption.

Extent of Absorption. The measured noninfinity estimate closest to that of AUC0–INF, based upon both its percentage infinity value and the test/reference (*T/R*) ratio of the means, was AUC0–LAST (Table IV). The relative residual error defined by the ANOVA (the mean square error of the residual term divided by the grand mean) ranged from 41.92% (AUC10M) to 54.07% (AUC0–LAST). Despite its large relative residual error, the 90% confidence interval for AUC0–LAST provided the best approximation of the 90% confidence interval defined by AUC0–INF.

For any given fsd, the confidence interval was markedly influenced by the size of the reference mean. For example, the danazol confidence interval for AUC0–INF had a width of 37 units despite its 44% fsd and an *N* of only 23 subjects (i.e., that received both treatments). In contrast, the confidence interval associated with the danazol AUC10M had a lower fsd and a substantially larger *N* value but its width was only slightly less than that for AUC0–INF. This is attributable to the presence of a smaller reference value, resulting in both upper and lower limits being larger than those for AUC0–INF.

Table III. Mean Pharmacokinetic Parameters and the Corresponding Intersubject fsd for the Danazol, Baclofen, and Oxazepam Data Sets

Drug	AUC0–INF (ng · hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	Half-life (hr)
Danazol				
Test	476.8	63.4	2.0	11.2
	(51.8)	(377.5)	(1644.2)	(1306.5)
Ref	568.3	56.6	2.2	12.9
	(68.2)	(52.0)	(62.0)	(72.2)
Baclofen				
Test	1530.6	317.6	1.5	3.4
	(32.0)	(31.7)	(51.3)	(38.7)
Ref	1477.9	302.9	1.6	3.4
	(39.3)	(35.9)	(31.1)	(30.9)
Oxazepam				
Test	3673.2	325.7	3.4	8.1
	(37.1)	(32.3)	(40.1)	(25.6)
Ref	3306.6	233.9	3.6	10.9
	(34.9)	(39.9)	(39.3)	(31.9)

Baclofen

Rate of Absorption. The two baclofen-containing products were similar with regard to their C_{max} and T_{max} values as well as for the intersubject variability associated with these values (Table III).

Extent of Absorption. There was little difference in the magnitude of the fsd-ANOVA regardless of whether the AUC was measured to hr 6 or to the last detectable concentration. However, the error did increase when the area was extrapolated from the last measured concentration to time infinity. Consequently, of the three area estimates, AUC0–INF was associated with the widest confidence interval (Table V). Based upon its percentage infinity value, AUC0–LAST provided the closest approximation of AUC0–INF. However, as seen with the simulated data, when confidence intervals for AUC0–LAST resembled those for AUCTM, both estimates had a similar performance. For baclofen, the *T/R* ratios were similar across all three AUC values. With the exception of AUC0–INF, the fsd-ANOVA remained under 10% across all estimates. For baclofen, the confidence intervals exhibited approximately equal upper and lower bounds across all three estimates due to its relatively short half-life. Therefore, a greater percentage of AUC0–INF was estimated over the 6-hr time period than was the case for danazol, which had an 11-hr half-life.

Oxazepam

Rate of absorption. Unlike baclofen and danazol, there was a statistically significant interproduct difference in ab-

Table IV. Summary of Factors Involved in the Determination of 90% Confidence Intervals Around the Difference in Treatment Means Relative to the Reference Product for the Danazol Data Set[a]

Parameter	N_R	N_T	$N(T-R)$	Test	Ref	% Inf T	% Inf R	T/R	Fsd ANOVA	90% CI	Width CI
AUC0–INF	27	27	23	476.8	568.0	1.00	1.00	0.84	44.06	65.4–102.4	37.0
AUC0–LAST	35	35	35	397.9	478.0	0.84	0.84	0.83	54.07	63.3–103.1	39.8
AUC10M	34	34	33	266.2	278.0	0.56	0.49	0.96	41.92	78.5–112.8	34.3

[a] N_R = number of subjects included in the determination of the reference mean; N_T = number of subjects included in the determination of the test mean; $N(T-R)$ = number of subjects receiving both treatments included in the interproduct comparison; % Inf T = the ratio of AUC0–LAST or AUCTM divided by AUC0–INF for the test product; % Inf R = the ratio of AUC0–LAST or AUCTM divided by AUC0–INF for the reference product; fsd ANOVA = the residual mean square error divided by the grand mean from the ANOVA; 90% CI = confidence interval of the difference between the product means expressed in relation to the reference mean; T/R = test mean/reference mean for the parameter of interest.

sorption rates of the test and reference oxazepam products. The mean absorption rate constant (k_a) of the generic product was 1.857 hr^{-1}, while that of the reference was 1.173 hr^{-1} (ratio = 1.58). The products differed by 39.2% in their C_{max} values. T_{max} values were similar (Table III).

Extent of Absorption. The width and direction of the 90% confidence intervals differed according to whether these intervals were based upon measured or infinity estimates (Table VI). This result is unlike that previously encountered with either baclofen or danazol and most probably reflects the large interproduct difference in oxazepam absorption rates. It should be noted that despite the disparity in product absorption rates, drug absorption should have been completed prior to hr 60 (based upon the estimated absorption rate constants). In addition, the ratio of k_a/K_e for both the test and the reference products exceeded 18.0. Nonetheless, the interproduct difference at hr 60 was significantly different from that observed at AUC0–INF (based upon profile analysis, $P < 0.05$).

With regard to the relative residual error, the fsd-ANOVA ranged from 10 to 14%. The error tended to decrease as the duration of blood sampling increased. The width of the 90% confidence intervals decreased accordingly.

In general, the widths of the 90% confidence intervals of the oxazepam data set for the measured values were wider than those for AUC0–INF. These differences can be attributed to a higher fsd since most of the drug had been absorbed by hr 20. The presence of smaller reference values of the measured estimates further contributed to the widening of the confidence intervals.

DISCUSSION

Until now, the accuracy of estimating noninfinity AUC values, and hence drug product bioavailability, was thought to be related primarily to the duration of blood sampling (1,10,11). However, the magnitude of the relative residual errors associated with these estimates is essential to the statistical analysis of bioequivalence.

The two one-sided test procedure for determining the 90% confidence intervals relative to some reference mean is a statistical procedure frequently employed in the evaluation of product bioequivalence (20). The width and direction of this statistic are influenced by the number of subjects included in the estimate (N), the size of the reference mean, the ratio of the test/reference AUC value (T/R), and the magnitude of the residual error associated with the estimate of the difference (20). The current study indicates that the relationship between each of these factors and any noninfinity AUC estimate is a function of both the magnitude of the relative residual error associated with a specific drug entity and the comparability of the absorption rates of the products being investigated.

The degree of similarity in the relative residual errors across the noninfinity AUC estimates was a function of the product's intrasubject variability. The greatest change in the fsd from the ANOVA (i.e., 54%) was seen with the danazol data set. Conversely, the error associated with the oxazepam and baclofen data sets were relatively small (approximately 8–14%). Nonetheless, the corresponding confidence intervals for the three parameters showed considerable variability. This was due to the use of smaller reference values (a

Table V. Summary of Factors Involved in the Determination of 90% Confidence Intervals Around the Difference in Treatment Means Relative to the Reference Product for the Baclofen Data Set[a]

Parameter	N_R	N_T	$N(T-R)$	Test	Ref	% Inf T	% Inf R	T/R	Fsd ANOVA	90% CI	Width CI
AUC0–INF	29	29	29	1530.6	1477.9	1.00	1.00	1.04	14.89	96.6–110.5	13.9
AUC0–LAST	29	29	29	1308.3	1245.1	0.85	0.84	1.05	9.89	100.5–109.6	9.1
AUC6M	29	29	29	1001.68	946.1	0.65	0.64	1.06	8.56	101.9–109.8	7.9

[a] Abbreviations defined in Table IV, footnote *a*.

Table VI. Summary of Factors Involved in the determination of 90% Confidence Intervals Around the Difference in Treatment Means Relative to the Reference Product for the Oxazepam Data Set[a]

Parameter	N_R	N_T	$N(T-R)$	Test	Ref	% Inf T	% Inf R	T/R	Fsd ANOVA	90% CI	Width CI
AUC0–INF	28	28	28	3676.2	3306.6	1.00	1.00	1.11	10.36	106.1–116.0	9.9
AUC0–LAST	28	28	28	3491.4	3058.7	0.95	0.93	1.14	10.70	108.9–119.3	10.4
AUC6M	28	28	28	2915.0	2204.4	0.79	0.67	1.32	14.20	124.3–140.2	15.9

[a] Abbreviations defined in Table IV, footnote *a*.

smaller percentage of the infinity value) as the defined AUC parameter. In the case of the danazol, in addition to the change in the reference mean, there was also a change in N. This was due to missing subject samples and the inability to estimate accurately a "log-linear phase" in all study subjects, the latter being attributable to the presence of secondary absorption maxima.

The generation of data subsets can potentially alter a bioequivalence decision. Therefore, it is imperative that bioequivalence decisions be established on the basis of all plasma-level data. In this light, the use of AUCTM estimates is ill advised since it necessitates the exclusion of a portion of the blood level–time data for subjects with long drug elimination half-lives from the bioequivalence comparison. Similarly, the use of AUC0–INF should be avoided if only a portion of the study subjects demonstrates a terminal log-linear phase. Therefore, the use of AUC0–LAST may be warranted whenever bioequivalence comparisons based on the infinity estimate uses less than the entire subject population.

The outcome of the oxazepam profile analysis was not consistent with that predicted by Lovering *et al.* (10) or Wagner (11). Although blood sampling extended well beyond the estimated absorption phase of both the test and the reference product and exceeded three times the estimated elimination half-life of the drug, the magnitude of the difference in the AUC of the test and the reference products at AUC0–LAST was significantly greater than the interproduct difference defined at AUC0–INF. In addition, the k_a/K_e ratios exceeded 18.0, suggesting that the ratios obtained at hr 60 (which well exceeds three times the oxazepam elimination half-life) should adequately represent that ratio defined at time infinity (1). This outcome raises an additional problem which may discourage the use of partial AUC(s); i.e., the time at which pseudodistribution equilibrium has been obtained may not be accurately assessed (22). This inaccuracy can be particularly problematic when assessing the relative bioavailability of products exhibiting dissimilar absorption rates.

The results of this investigation indicate that when AUC0–INF cannot be obtained or when the use of AUC0–INF results in a substantial loss of study subjects, the relative bioavailability of two or more drug products is best assessed by that noninfinite AUC estimate which fulfills the following criteria:

(1) does not result in the truncation of the available data,
(2) provides data well within the elimination phase of both drug products, and
(3) allows for full expression of the uniqueness of the individual time–concentration profiles.

The estimate which best fulfills all of the above criteria is AUC0–LAST. Accordingly, the confidence intervals associated with AUC0–LAST consistently provide the best estimate of those intervals defining the difference in product bioavailability at time infinity. Therefore, we recommend the use of AUC0–LAST whenever AUC0–INF cannot be adequately established.

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REFERENCES

1. M. Gibaldi and D. Perrier. In *Pharmacokinetics*, 2nd Ed., Marcel Dekker, New York, 1982.
2. F. Hatch, K. McKellop, G. Hansen, and T. MacGregor. Relative bioavailability of metaproterenol in humans utilizing a single dose, stable isotope approach. *J. Pharm. Sci.* 75:886–890 (1986).
3. M.-L. Aitio, H. Allonen, J. Kanto, and R. Mantyla. The pharmacokinetics of disopyramide and mono-N-dealkyl-disopyramide in humans. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 20:219–226 (1982).
4. M. Kraml, D. R. Hicks, M. McKean, J. Panagides, and J. Furst. The pharmacokinetics of etodolac in serum and synovial fluid of patients with arthritis. *Clin. Pharmacol. Ther.* 43:571–576 (1988).
5. A. T. Tembo, M. R. Hallmark, E. Sakmar, H. G. Bachmann, D. J. Weidler, and J. G. Wagner. Bioavailability of prednisolone tablets. *J. Pharmacokinet. Biopharm.* 5:257–270 (1977).
6. A. B. Straughn, G. C. Wood, G. Gursharan, and M. C. Meyer. Bioavailability of seven furosemide tablets in man. *Biopharm. Drug Disp.* 7:113–120 (1986).
7. F. Sorgel, J. Hasegawa, E. T. Lin, and R. L. Williams. Oral triamterene disposition. *Clin. Pharmacol. Ther.* 38:306–312 (1985).
8. R. K. Ferguson, P. H. Vlasses, J. R. Koplin, G. I. Holmes, P. Huber, J. Demetriades, and W. B. Abrams. Relationship among timolol doses, plasma concentrations and B-adrenoceptor blocking activity. *Br. J. Clin. Pharmacol.* 14:719–725 (1982).
9. K. Onoyama, F. Nanishi, S. Okuda, Y. Oh, M. Fujishima, M. Tateno, and T. Omae. Pharmacokinetics of a new angiotensin I converting enzyme inhibitor (delapril) in patients with deteriorated kidney function and in normal control subjects. *Clin. Pharmacol. Ther.* 43:242–249 (1988).
10. E. G. Lovering, I. J. McGilveray, I. McMillan, and W. Tostowaryk. Comparative bioavailabilities from truncated blood level curves. *J. Pharm. Sci.* 64:1521–1524 (1975).
11. J. G. Wagner. An overview of the analysis and interpretation of bioavailability studies in man. *Pharmacology* 8:102–117 (1972).
12. M. Berman and M. Weiss. *User's Manual for SAAM*, National Institutes of Health, Bethesda, Md., 1974.

13. W. D. Hooper, G. R. Cannell, and R. G. Dickinson. Sensitive and selective assay of danazol in plasma by high-performance liquid chromatography. *J. Chromatogr.* **416**:347–352 (1987).
14. G. A. Nygard, L. J. Lovett, G. R. Erdmann, and S. K. W. Khalil. Analysis of danazol in serum using high-performance liquid chromatography. *J. Chromatogr.* **415**:438–444 (1987).
15. P. M. Harrison, A. M. Tonkin, and A. J. McLean. Determination of 4-amino-3(p-chlorophenyl)butyric acid (baclofen) in plasma by high-performance liquid chromatography. *J. Chromatogr.* **339**:424–428 (1985).
16. K. Tada, T. Moroji, R. Sekiguchi, H. Motomuta, and T. Noguchi. Liquid-chromatographic assay of diazepam and its major metabolites in serum, and application to pharmacokinetic study of high doses of diazepam in schizophrenics. *Clin. Chem.* **10**:1712–1715 (1985).
18. K. Yamaoka, T. Nakagawa, and T. Uno. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J. Pharmacokin. Biopharm.* **6**:165–175 (1978).
19. G. W. Snedecor and W. C. Cochran. *Statistical Methods,* Iowa State University Press, Ames, 1976.
20. D. J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.* **15**:657–680 (1987).
21. D. F. Morrison. In *Multivariate Statistical Methods,* McGraw–Hill, Toronto, Canada, 1967.
22. R. A. Ronfeld and L. Z. Benet. Interpretation of plasma concentration-time curves after oral dosing. *J. Pharm. Sci.* **66**:178–180 (1977).