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The Degrees of Correlation in Bioavailability Parameters and the Confidence Regions in Bioequivalence Study

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ABSTRACT

The parameters to define the shape of the 1-α confidence ellipse constructed by the C_{max} and AUC_{∞}, the physical meanings of the shape of the ellipse, correlation of the C_{max} and AUC_{∞}, and confidence regions of two 95% confidence intervals and the 90% confidence ellipse was described and discussed. The ratio of the lengths of the major and minor axes for the confidence ellipse was a proportional function of the coefficient of correlation between the two relevant bioavailability variables. The degree of correlation could vary significantly from one bioequivalence study to another. The degree of correlation has great impact on the probability of confidence region and, hence, in univariate analysis each bioequivalence decision-making would be unavoidably based on the different probability. Examples of the bioequivalence study of nine drugs were demonstrated. In order to assess bioequivalence with a consistent probability, the bivariate method using two 90% confidence ellipses of reference and test products is proposed. Since each available statistical method has its limitation and shortcoming, it is desirable to evaluate bioequivalence using multiple assessment methods.

Key words : Correlation, C_{max}, AUC_{∞}, Confidence ellipse, Confidence region.

INTRODUCTION

In a preceding paper[2], some shortcomings of the conventional univariate approach in testing the bioequivalence of drug products were discussed. The report also presented a novel approach, using the bivariate confidence ellipse method to assess bioequivalence. The two problems associated with the use of univariate analysis are : (1)In the current guidelines, the C_{max} and AUC_{∞} or their log-transformed data are tested separately to establish each 90% confidence interval of the difference of means. The 90% confidence interval of each of the two variables when considered simultaneously, define a rectangular area in the plain. If the C_{max} and AUC_{∞} were independent, then the rectangular area would cover the true population mean difference with probability range of 0.81 to 0.9[3]. However, the peak plasma concentration C_{max} and the total area under the concentration-time curve AUC_{∞} are not independent variables and they must be considered simultaneously for the

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bioavailability of a drug product. Hence, the probability of a confidence region based on two confidence intervals would not be within the range of 0.81 to 0.9, and is ambiguous. In addition, the probability of such a confidence region would be significantly different along with different degrees of correlation between the two variables. Therefore, with the univariate method, it might be impossible to avoid an inconsistent probability for decision-making in the bioequivalence test. (2)In recent years, the log-transformation of bioavailability data before the analysis of variance has been adopted by regulatory agencies to correct the possible nonadditive nature of C_{max} and AUC_{∞} [4,5]. However, as it was pointed out by Westlake[6], the log-transformation of the AUC_{∞} or C_{max} will not guarantee a relationship that is strictly additive. Metzler[7] suggested that bioavailability data sets are very seldom large enough to use statistical tests to determine distribution of the data, and that transformation of data may cause problems in interpretation of results. Dighe and Adams[8] also reported that analyses performed on untransformed data should be routine in bioequivalence study. Chow et al.[9] pointed out that the log-transformed data may not follow a normal distribution due to unknown distributions of the transformed random subject effects. Distribution of the transformed data for a different formulation may be of a different type due to different distributions of transformed random subject effects. Liu and Weng[10] also gave a comprehensive comparison of the probability of concluding bioequivalence between the raw and the log-transformed data. It seems that the adoption of log-transformation in the test of bioequivalence may be based on the political and economical considerations, rather than upon scientific consensus.

On the other hand, in the confidence ellipse method, bivariate normal distribution is assumed[3]. If the C_{max} and AUC_{∞} were confirmed to show bivariate log-normal distribution, the assumption may be satisfied by the log-transformation of the C_{max} and AUC_{∞}. Further, the confidence region established by the confidence ellipse is exactly $1-\alpha$ confidence, so that probability in the bioequivalence dicision-making would be consistent for all studies. This report presents the parameters which define the characteristic shape of the $1-\alpha$ confidence ellipse and the physical meanings of the elliptical shape, and demonstrates that the degrees of correlation between C_{max} and AUC_{∞} can vary significantly from one bioequivalence study to another. The significantly different areas of the confidence region constructed by the two 95% confidence intervals (with lower bound of 90.25% confidence region for two independent variables) and by the 90% confidence ellipse are also demonstrated.

MATERIALS AND METHODS

Bioavailability Data

The C_{max} and AUC_{∞} of nine drugs in twelve crossover studies reported in the preceding paper[2] were used.

Transformation of Data

To facilitate the comparison among the studies, the data of C_{max} and AUC_{∞} were standardized after the log-transformation. The standardization of the data was carried out by using equation 1.

$$Z=\frac{Xi-\bar{X}}{S} \qquad (1)$$

Where Xi: the i-th log-transformed sample data.
$\bar{X}$: the mean of log-transformed sample data.
S : the standard deviation of log-tansformed data.

Confidence Intervals

The 95% confidence intervals were computed by the conventional method : Mean $\pm$ $t_{(n-1,0.05)}$ (standard error), where $t_{(n-1,0.05)}$ was Student's t value for degrees of freedom n–1 and α

$=0.05$(two-sided) and n was the size of study.

Bivariate Confidence Ellipse

Assuming that the bioavailability of a drug product can be defined simultaneously by the two correlated variables (X_1, X_2), and under the normality assumption, Hotelling's T^2 statistic can be written as the equation 2[11]. The equation 2 can also be rearranged to give the equation 3[12].

$$n(X_1-\bar{X},\ X_2-\bar{X}_2)\begin{bmatrix} S_1^2 & S_{12} \\ S_{12} & S_2^2 \end{bmatrix}^{-1}\begin{bmatrix} X_1-\bar{X}_1 \\ X_2-\bar{X}_2 \end{bmatrix}$$

$$=\frac{2(n-1)}{(n-2)}F_{(2,n-2,1-\alpha)} \qquad (2)$$

$$\frac{n(n-2)}{2(n-2)F_{(2,n-2,1-\alpha)}}\frac{1}{\triangle}[S_2^2(X_1-\bar{X}_1)^2-2S_{12}$$
$$(X_1-\bar{X}_1)\ (X_2-\bar{X}_2)+S_1^2(X_2-\bar{X}_2)^2]=1 \qquad (3)$$

where $\triangle = S_1^2S_2^2-S_{12}^2$

$S_j^2 = \sum_{i=1}^{n}(X_{ji}-X_j)^2 \qquad j=1, 2$

$S_{12} = \sum_{i=1}^{n}(X_{1i}-\bar{X}_1)\ (X_{2i}-\bar{X}_2)$

n = the size of study.

X_1 = C_{max} after transformation.

X_2 = AUC_∞ after transformation.

$F_{(2,n-2,1-\alpha)}$: $1-\alpha$ quantile of F distribution with degrees of freedom 2 and n–2.

The equation 3 represents the $1-\alpha$ confidence region for the population mean vector of X_1 and X_2, and it is an ellipse. The shape of an ellipse can be characterized by the ratio of the lengths of its major and minor axes, and the linear equations of the major and minor axes. The lengths of the major and minor axes are, respectively, the eigenvalues λ_1 and λ_2 found from the variance-covariance matrix as shown in equation 4. The equations 5 and 6 depict the eigenvalues of λ_1 and λ_2.

$$\begin{bmatrix} S_1^2-\lambda & S_{12} \\ S_{21} & S_2^2-\lambda \end{bmatrix}=0 \qquad \text{where } S_{12}=S_{21} \quad (4)$$

$$\lambda_1=\frac{1}{2}[(S_1^2+S_2^2)+\sqrt{(S_1^2+S_2^2)^2-4(S_1^2S_2^2-S_{12}^2)}] \qquad (5)$$

$$\lambda_2=\frac{1}{2}[(S_1^2+S_2^2)-\sqrt{(S_1^2+S_2^2)^2-4(S_1^2S_2^2-S_{12}^2)}] \qquad (6)$$

Since the major and minor axes are perpendicular to each other, the linear equations for the major and minor axes can be written as equations 7 and 8, respectively[3].

$$X_2=\bar{X}_2+\frac{S_{12}}{(\lambda_1-S_2^2)}(X_1-\bar{X}_1) \qquad (7)$$

$$X_2=\bar{X}_2-\frac{(\lambda_1-S_2^2)}{S_{12}}(X_1-\bar{X}_1) \qquad (8)$$

Degrees of Correlation

The degrees of correlation between X_1 and X_2 can be estimated by using the product-moment correlation coefficient (r_{12}), as equation 9 [13].

$$r_{12}=\frac{S_{12}}{S_1S_2} \qquad (9)$$

Since the standardized X_1 and X_2 were used to calculate the s_1, s_2 and s_{12}, s_1 would equal to s_2 so that the substitution of this relation into equations 5 and 6 gave equation 10.

$$\frac{\lambda_1}{\lambda_2}=\frac{1+|r_{12}|}{1-|r_{12}|} \qquad (10)$$

Equation 10 clearly indicated that the ratio of the lengths of the major and minor axes of the confidence ellipse was the function of the coefficient of correlation (r_{12}). Namely, the higher the degrees of correlation between the two variables, the greater the values of the ratio. If the two variables were independent, then r_{12} would be 0, and the ratio would approach 1.0. Hence, the confidence region was represented by a circle. On the orther hand, if the two variables were highly correlated, the ratio would be very large, then a very narrow, elongated ellipse should be formed. Thus, the magnitude of the ratio reflected the degrees of correlation. For instance, if the value of ratio is greater than 19, the coefficient of correlation will be higher than 0.9 (Equation 10).

Table 1. Bioavailability Data and Transformed Data of Atenolol Tablets.
Atenolol 100 mg tablets

Reference product				Test product			
C_{max}	Trans. Data	AUC_x	Trans. Data	C_{max}	Trans. Data	AUC_x	Trans. Data
0.344	–0.535	3.783	–0.295	0.389	–1.300	3.848	–1.323
0.577	0.492	5.042	0.419	0.552	0.073	5.733	0.582
0.567	0.457	5.306	0.545	0.733	1.186	6.585	1.244
0.924	1.427	6.482	1.042	0.726	1.148	5.632	0.497
0.314	–0.716	3.721	–0.336	0.529	–0.094	6.367	1.084
0.189	–1.724	1.850	–2.072	0.554	0.087	4.630	–0.439
0.401	–0.231	3.858	–0.246	0.606	0.439	4.689	–0.379
0.684	0.830	6.224	0.942	0.366	–1.539	3.894	–1.266

C_{max} : mcg/ml, AUC_x : (mcg/ml)h, Trans. Data: log and standardization.

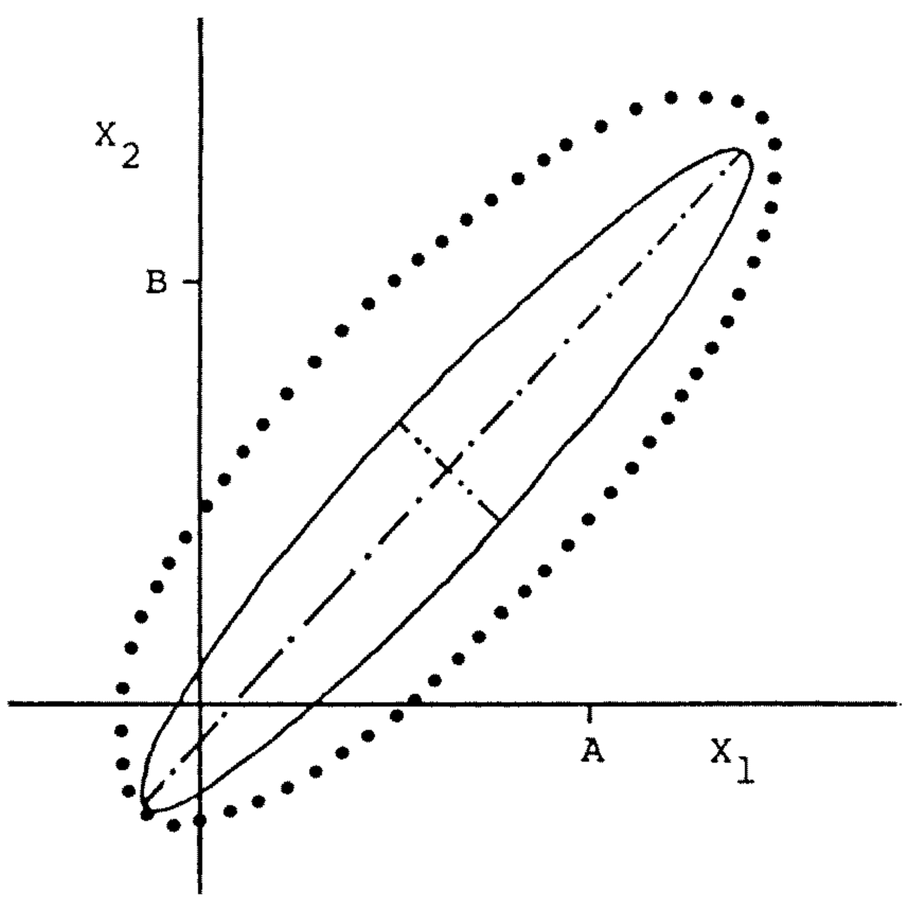

Figure 1. The 90% Confidence Ellipses of Atenolol. solid line: reference product, dotted line: test product, Origin (–1.72, –2.07), A(1.43, –2.07), B(–1.72, 1.04), $-\cdot-$:λ_1 $-\cdot\cdot-$: λ_2, X_1: transformed C_{max}, X_2: transformed AUC_∞.

Unbiased Estimate of Population Correlation Coefficient (ρ_{12})

In general, the sample size (n) of the bioequivalence study was rather small, and hence r_{12} is slightly biased and underestimates population correlation coefficient ρ_{12}. A correction suggested by Kendall and Stuart[14] for the bivariate normal distribution as shown in equation 11 was also performed to obtain the unbiased estimate of ρ_{12} (r_{12}^*).

$$r_{12}^* = r_{12}\left[1+\frac{1-r_{12}^2}{2(n-4)}\right] \quad (11)$$

RESULTS AND DISCUSSION

Numerical Examples

Two bioequivalence studies of atenolol and theophylline tablets were illustrated. Table 1 depicts the C_{max} and AUC_∞ of atenolol, and their transformed data. Figure 1 shows the 90% confidence ellipses of the reference and test products. The results of the analysis are depicted in Table 2. It is evident that the apparent coefficient of correlation for the test product was smaller than that of the reference product. This relationship was also reflected in the magnitude of the ratios of the lengths of major and minor axes. If the study was under well control, then the result might suggest the greater variability in bioavailability of the test product.

The C_{max} and AUC_∞ of theopylline, and their transformed data are depicted in Table 3. The 90% confidence ellipses of the reference and test products are shown in Figure 2. Table 4 depicts the results of analysis. The shapes of the two confidence ellipses were quite different and an anomalistic negative coefficient of correlation was observed with the data of the reference pro-

Table 2. The Shapes of 90% Confidence Ellipse of Atenolol.

	Reference product		Test product	
	a	b	a	b
Major axis	1.504	0.329	1.547	0.305
Minor axis	7.307	–3.037	7.733	–3.284
λ_1	13.752		12.453	
λ_2	0.248		1.547	
λ_1/λ_2	55.4		8.1	
r_{12}	0.9645		0.7790	
r_{12}^*	0.9729		0.8173	

Equation form: $X_2=a+bX_1$, X_1: transformed C_{max},

X_2: transformed AUC_∞. λ_1 and λ_2: the lengths of major and minor axes,

r_{12}: correlation coefficient, r_{12}^*: unbiased estimate of population correlation coefficient.

Table 3. Bioavailability Data and Transformed Data of Theophylline Tablets.
Theophylline 350 mg tablets

Reference product				Test product			
C_{max}	Trans. Data	AUC_∞	Trans. Data	C_{max}	Trans. Data	AUC_∞	Trans. Data
5.75	0.494	104.72	0.919	3.41	0.241	148.70	1.183
6.40	1.065	83.97	0.008	4.88	0.794	100.55	0.546
5.38	0.140	88.10	0.206	3.09	0.089	96.74	0.483
5.35	0.110	83.32	–0.024	4.56	0.690	81.60	0.205
5.50	0.257	48.19	–2.284	1.00	–1.653	31.91	–1.325
5.01	–0.240	96.13	0.566	5.04	0.844	87.26	0.314
4.71	–0.569	86.29	0.120	1.88	–0.678	51.06	–0.559
3.28	–2.498	96.17	0.568	4.33	0.610	92.78	0.414
5.61	0.363	64.24	–1.097	0.96	–1.716	20.77	–2.025
6.18	0.879	107.25	1.018	4.83	0.779	115.00	0.764

C_{max} : mcg/ml, AUC_∞ : (mcg/ml)h.

Table 4. The Shapes of 90% Confidence Ellipse of Theophylline.

	Reference product		Test product	
	a	b	a	b
Major axis	2.55	–1.07	1.48	0.321
Minor axis	–21.06	9.346	10.07	–3.116
λ_1	10.225		17.062	
λ_2	7.775		0.938	
λ_1/λ_2	1.3		18.2	
r_{12}	–0.1361		0.8958	
r_{12}^*	–0.1473		0.9105	

Equation form: $X_2=a+bX_1$, X_1: transformed C_{max}, X_2: transformed AUC_∞.

duct. This anomaly suggested that there must be something wrong in the study. The shape of the ellipse and the correlation coefficient for the test product were reasonable, but the sign of the correlation coefficient for the reference product was abnormal since in pharmacokinetics the C_{max} and AUC_{∞} should be positively correlated. The result should call for careful reexamination of the whole study including the quality of the reference product, blood sampling schedule, medical and analytical control.

Variability of Correlation Between C_{max} and AUC_{∞}

Table 5 depicts the summary of the shape of confidence ellipse and the correlation analysis for the remained studies. It is intriguing to note that the correlation was good in cephadrine (2) test product, but it was very poor in the reference product. The reverse situation was also seen in gemfibrozil(1). A significant difference of correlation observed in a crossover study should call the attention of the investigator to need for careful reexamination of the study. The problem might come from significant differences in the quality of the products, the blood collection time schedule, medical or analytical problems, the carry-over effect or the outlier effect. Thus, correlation analysis may provide insightful information into studies. It is very important to note

Table 5. Summary of the Shapes of 90% Confidence Ellipse.

	Reference product				Testproduct			
	Major	axis	Minor	axis	Mjaor	axis	Minor	axis
	a	b	a	b	a	b	a	b
Cefazoline	1.10	0.11	23.21	–8.92	0.84	0.22	12.50	–4.54
Cephradine (1)	1.33	0.21	7.40	–4.87	1.40	0.14	9.97	–7.03
Cephradine (2)	1.17	0.18	11.34	–5.54	0.91	0.33	6.96	–3.07
Famotidine (1)	0.69	0.31	8.35	–3.22	0.67	0.32	8.15	–3.13
Famotidine (2)	1.01	0.33	8.78	–3.07	1.01	0.32	8.82	–3.09
Gemfibrozil (1)	1.52	0.31	9.33	–3.24	1.70	0.22	12.15	–4.57
Gemfibrozil (2)	1.30	0.31	6.60	–3.24	1.31	0.31	6.66	–3.28
Penthydroxifylline	1.07	0.33	9.63	–3.07	1.06	0.33	9.55	–3.04
Phenylpropanolamine	0.90	0.26	7.99	–3.84	0.90	0.26	7.95	–3.82
Ranitidine	1.42	0.31	5.97	–3.18	1.46	0.28	6.43	–3.54

	Reference product			Test product		
	λ_1/λ_2	r_{12}	r_{12}^*	λ_1/λ_2	r_{12}	r_{12}^*
Cefazoline	1.3	0.1445	0.1546	2.3	0.3932	0.4169
Cephradine (1)	2.1	0.3481	0.3736	1.5	0.1990	0.2149
Cephradine (2)	1.8	0.2825	0.3042	28.1	0.9313	0.9416
Famotidine (1)	10.2	0.8214	0.8362	16.6	0.8864	0.8969
Famotidine (2)	28.9	0.9331	0.9406	24.1	0.9205	0.9292
Gemfibrozil (1)	8.1	0.7814	0.8004	2.3	0.3885	0.4091
Gemfibrozil (2)	9.4	0.8084	0.8284	8.2	0.7821	0.8038
Penthydroxifylline	28.1	0.9313	0.9375	49.2	0.9602	0.9639
Phenylpropanolamine	3.4	0.5431	0.5814	3.4	0.5490	0.5873
Ranitidine	12.0	0.8467	0.8667	4.7	0.6514	0.6826

Equation form: $X_2 = a + bX_1$, X_1: transformed C_{max}, X_2: transformed AUC_{∞}.

that the degree of correlation between bioavailability relevant parameters could vary significantly from one study to another. For instance, the r_{12} could be as low as 0.1445 in the cefazoline study and could be as high as 0.9602 in the study of penthydroxifylline. This would raise a serious problem when conventional univariate analysis is applied for the bioequivalence decision, since the degree of correlation has great impact on the probability of the confidence region. Each bioequivalence study may have a significantly different degree of correlation, and hence each bioequivalence decision-making would be unavoidably based on different probability. In the confidence ellipse approach, there would be no such a problem since the degree of correlation was considered in the variance-covariance matrix. Therefore, the bioequivalence of drug products can be justified by a consistent 1-α confidence region for each study.

Different Confidence Regions Between Two 95% Confidence Intervals and 90% Confidence Ellipse

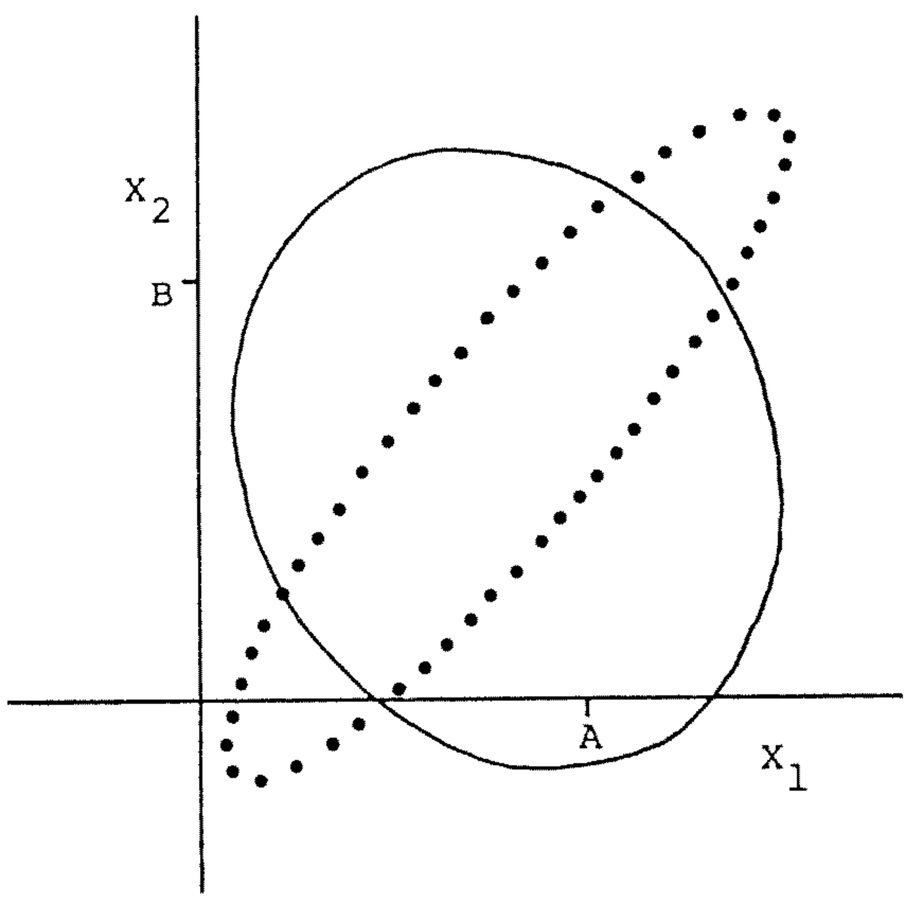

Figure 2. The 90% Confidence Ellipses of Theophylline.
solid line: reference product, dotted line: test product, Origin (–2.50, –2.28), A(1.06, –2.28), B(–2.50, 1.02), X_1: transformed C_{max}, X_2: transformed AUC_∞.

Flury and Riedwyl[3] reported that the difference between the confidence region of the confidence ellipse and the two confidence intervals is greater the higher the variables are correlated because the confidence ellipse tends to become quite narrow and elongated with increasing correlation. As a result, the area covered by the rectangle (two confidence intervals) and by the ellipse would be significantly different. Therefore, it is probable that some highly correlated bioequivalence studies which were claimed to be not bioequivalent using the 95% confidence interval test, but they might be bioequivalent using the 90% confidence ellipse method. One such example was the case of gemfibrozil(2) (both $r_{12}^{*}>0.8$) demonstrated in the preceding report[2]. On the other hand, the reverse situation may also be possible. Figures 3 and 4 illustrate respectively the confidence regions for the reference products of atenolol and gemfibrozil(2). The true probabilities represented by the rectangular areas in the figures were not clear. The ratios of the area of the rectangle/ellipse were respectively 2.8/5.9 〔atenolol〕 and

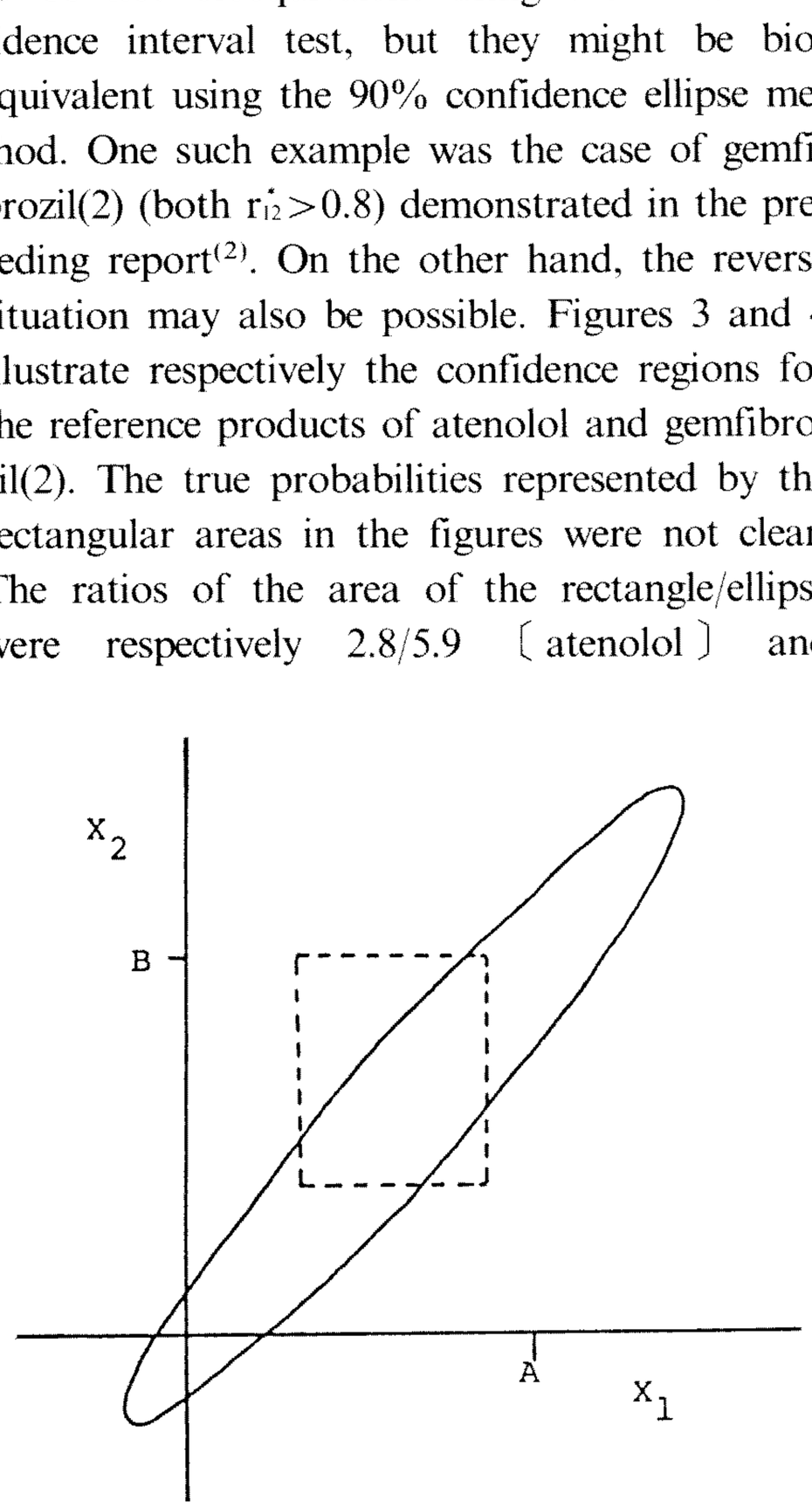

Figure 3. The 90% Confidence Region of Atenolol Reference Product.
solid line: 90% confidence ellipse, dotted line: two 95% confidence intervals. Origin (–1.72, –2.07), A (1.43, –2.07), B(–1.72, 1.04), X_1: transformed C_{max}, X_2: transformed AUC_∞.

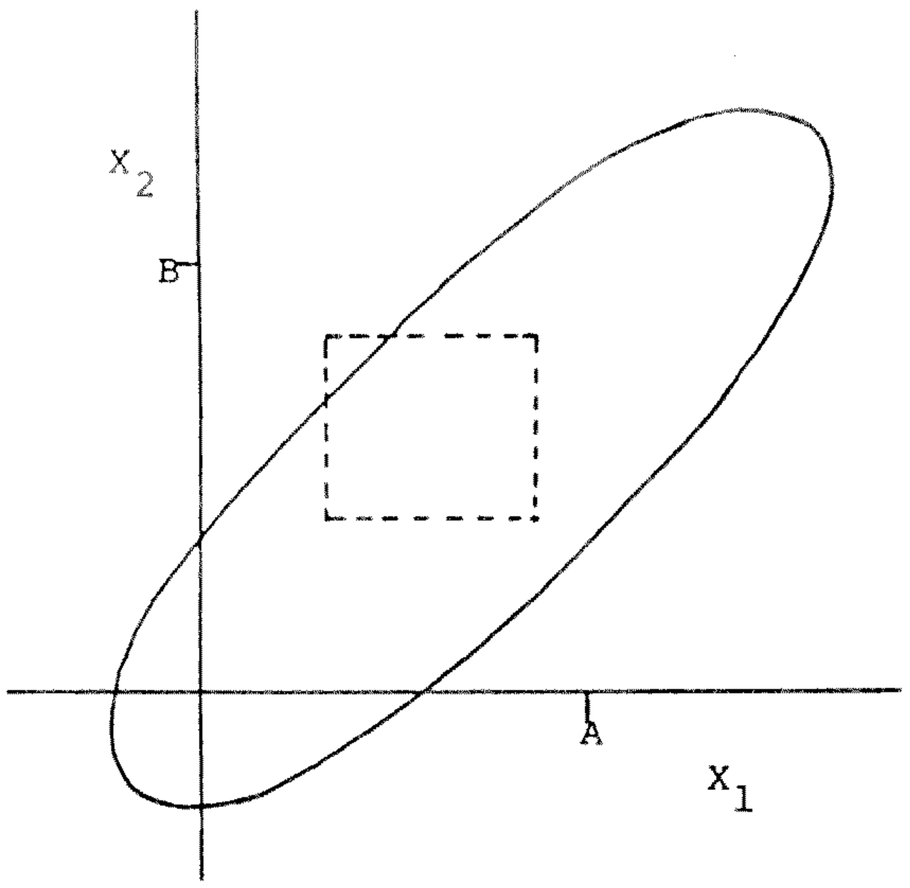

Figure 4. The 90% Confidence Region of Gemfibrozil (2) Reference Product.
solid line: 90% confidence ellipse, dotted line: two 95% confidence intervals. Origin (–1.49, –1.76), A (1.05, –1.76), B(–1.49, 1.34), X_1: transformed C_{max}, X_2: transformed AUC_∞.

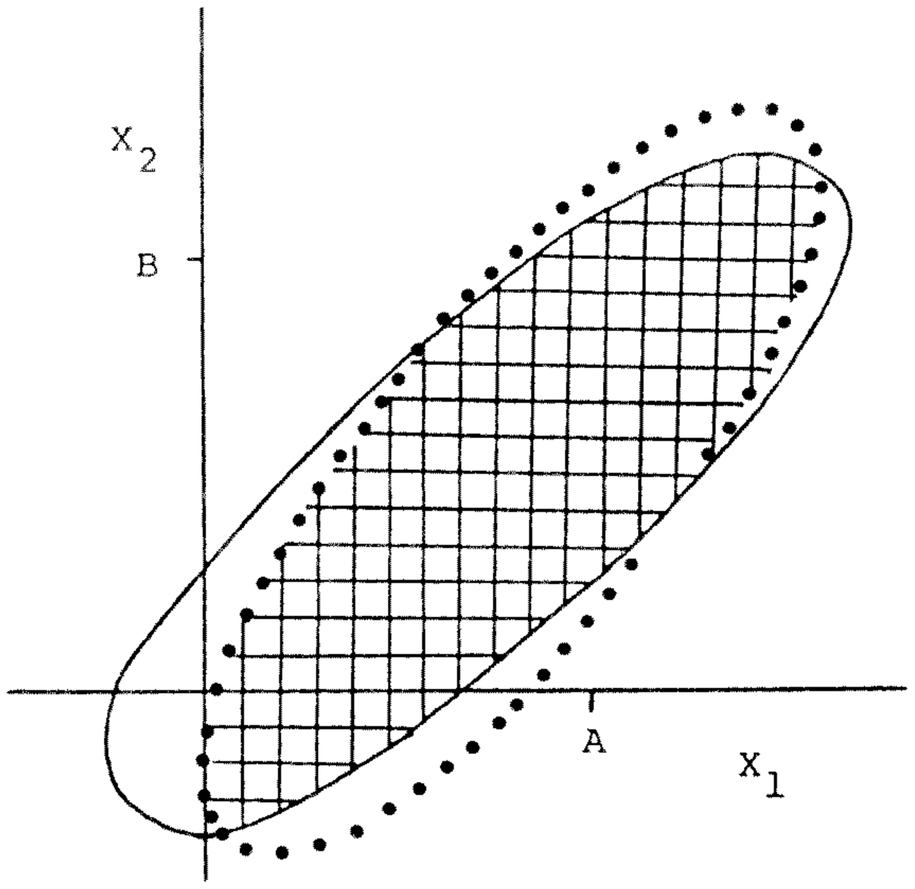

Figure 5. The Fraction of Overlapping Between Two 90% Confidence Ellipses.
solid line: reference product, dotted line: test product, Origin (2.25, 3.38), A(3.01, 3.38), B(2.25, 3.39), X_1: ln C_{max}, X_2: ln AUC_∞.

1.8/11.2〔gemfibrozil(2)〕. The probability that each rectangle would cover the true population mean vector was apparently not 90.25% because of the correlation, and might be different in the two studies. Therefore, it is useful to propose that the specification test using the bivariate confidence ellipse method reported in the preceding paper[2] may be employed to examine whether the sample vectors of the reference and test products were from a common population. For instance, if all the sample vectors of the test product were contained in the 90% confidence ellipse constructed with the vectors of the reference product, then the bioequivalence between two products could be suggested with 90% confidence. In addition, the degrees of bioavailability similarity between two drug products may be elucidated by the fraction of overlap between the two 90% confidence ellipses of reference and test products. The fraction of overlap may reflect the probability that the estimated population mean vector of the test product is contained in the 90% confidence region of the estimated population mean vector of the reference product. The method to estimate the fraction of overlap was reported in a preceding paper[12]. In the case of gemfibrozil(2), the fraction of 90% confidence ellipse of test product overlap with that of the reference product was 0.822, as shown in Figure. 5 (with log-transformed C_{max} and AUC_∞, without standardization). The method of the degrees of similarity may provide a quantitative measure for evaluation of the similarity in the bioavailability between test and reference products. Thus, it can be used as an additional information to facilitate the biopharmaceutical, medical and regulatory justification to suggest the bioequivalence.

Advantages and Disadvantages of Bivariate Method

The bivariate confidence ellipse method has some unique characteristics superior to classical confidence interval method as discussed. However, the bivariate method also suffers from some disadvantages: (1) Since the confidence re

gions are computed separately for the test and reference products, the method does not take into account the structure of a crossover design. Thus, the resulting confidence region may contain nuisance parameters such as period and carry-over effects. The absence of period and carry-over effects may be mandatory in using bivariate method. (2) It uses both intersubject and intrasubject variabilities for the assessment of bioequivalence (covariance matrix). Thus, the method based on a larger variability may have a larger opportunity of concluding bioequivalence than classical confidence interval method. Since the evaluation of intrasubject variability is impossible both in univariate and bivariate methods using a standard 2×2 crossover design, the effect of intrasubject variability on the bioequivalence assessment may be the same in both methods. However, the variability of the least squares mean of sample is not considered in classical confidence interval method, but is incorporated in the assessment using bivariate method. Chow and Liu[15] showed when there is large variability in the least squares mean of the sample studied, the assessment of bioequivalence in average bioavailability by classical 90% confidence interval method may lead to significantly low level of assurance (lower than 90%). Therefore, bivariate mehtod (fraction of overlap) may be more reasonable than classical confidence interval method in this respect. (3) It heavily depends upon the normality assumption for the bivariate vector. The normality assumption of data in bioequivalence study may be a common problem in both univariate and bivariate methods, and is difficult to examine because of the small size of study.

CONCLUSION

It is obvious that the bioequivalence issue among the drug products is not a simple statistically dichotomous problem. The biopharmaceutical, medical and regulatory considerations should be involved in the decision-making. Since each available statistical method has its limitation and shortcoming, it is desirable to evaluate bioequivalence with multiple methods of assessment.

Further studies are especially required in this field.

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生體可用率有關的參數間之相關度及生體相等性試驗的可信區域

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摘　要

傳統上，判定二種藥劑是否具有生體相等性皆沿用簡易之單變數統計解析法。對C_{max}, AUC_{∞}等參數分別推定標準品和試驗品間之平均差異度的95%或90%可信間距作爲是否具有類同性之判定基準。

二個95%可信間距構成一可信區域。倘若C_{max}和AUC_{∞}互不相關，爲各自獨立之變數則此一可信區域涵蓋C_{max}和AUC_{∞}之推定母平均向量的下限機率爲$(0.95)^2 = 90.25\%$。但是在藥物動力學已知C_{max}及AUC_{∞}爲高度相關之參數，於是此一可信區域之機率隨相關度之大小而異。

本文以實例闡明在每一個生體相等性試驗，C_{max}和AUC_{∞}之相關度皆不同且差異頗大。因之，以簡易之單變數統計解析法來判定二種藥劑是否具有生體相等性所據的機率在各個試驗並不相同。由C_{max}和AUC_{∞}各別之95%可信間距構成之矩形可信區域顯然地有異於90%可信橢圓。90%可信橢圓正確地規範C_{max}和AUC_{∞}之推定母平均向量存在之90%可信區域而二個95%可信間距構成之矩形可信區域涵蓋推定母平均向量之可信機率到底有多大不但不清楚而且隨着不同之試驗而不同。

因此，若欲以明確而一致的可信機率爲基準來判定二種藥劑是否具有生體相等性，雙變數可信橢圓法是較合理可行的方法。然而，每一種統計分析方法皆有其缺陷，現階段生體相等性的判定最好參照多種分析方法的結果比較適宜。