Journal of Biopharmaceutical Statistics, 16: 385–392, 2006

ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543400600629906

Taylor & Francis
Taylor & Francis Group

ON THE ASSESSMENT OF DOSE PROPORTIONALITY: A COMPARISON OF TWO SLOPE APPROACHES

Bin Cheng
Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA

Shein-Chung Chow
Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA

Wei-Lun Su
Division of Basic Research, Koo Foundation, Sun Yat-Sen Cancer Center, Taipei, Taiwan

The problem for assessment of dose proportionality (or linearity) is studied. Various methods for assessment of dose proportionality (or linearity) such as ANOVA type F-test have been proposed. Cheng et al. (2006) proposed an alternative approach based on the slopes of adjacent dose levels under a crossover design. They showed that when dose proportionality (or linearity) cannot be established, their proposed slope approach is useful for evaluation of the degree of departure from dose proportionality (or linearity). In this article, we propose the use of slopes between the dose level and the initial dose (baseline), which we refer to as the baseline slope approach. The two slope approaches are compared under a parallel group design by means of an ANOVA type F-test and other tests. Simulation studies show that the proposed method has a satisfactory small sample performance.

Key Words: Adjacent slope approach; ANOVA *F*-test; Baseline slope approach; Dose proportionality.

1. INTRODUCTION

Before first-in-man clinical trial, dose-response studies in terms of pharmacokinetic (PK) parameters are often conducted not only to assess drug tolerance and safety but also to characterize dose-response curve with respect to efficacy. Rodda et al. (1988) indicated that the clinical investigation of the dose-response curve in terms of PK parameters can be classified into categories of 1) dose-ranging study, which estimates the minimum effective dose (MED) and maximum tolerable dose (MTD), 2) dose-response existence, and 3) dose-response

Received January 1, 2006; Accepted February 10, 2006
Address correspondence to Bin Cheng, Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY 10032, USA; Fax: (212) 342-1232; E-mail: bc2159@columbia.edu

characterization, which describes the shape of the dose-response curves and decides whether there is a clinically meaningful increase in response between the minimum effective and maximum tolerable doses. Ruberg (1995a,b) provided a comprehensive review of the designs, analyses, and interpretations of dose-response studies.

Among various types of dose-response relationships, dose proportionality (or linearity) is arguably the most desirable dose-response relationship between dose level and PK responses such as area under the blood or plasma concentration-time curve (AUC) due to its clear interpretation. For example, under the assumption of dose proportionality, we expect to see a doubled AUC if we double the dose. Besides, under the property of dose proportionality (or linearity), the PK responses can be easily predicted with various dose levels. Various methods for assessment of dose proportionality (or linearity), such as ANOVA type F-test, have been proposed in the literature (see also Chow and Liu, 2003). As pointed out by Law (2000), assessing departure from dose linearity is also of clinical importance when the dose proportionality (or linearity) cannot be established. Cheng et al. (2006) proposed a slope approach to test for a minor departure from dose linearity based on slopes calculated between the adjacent dose levels. In this article, alternatively, we propose using the slopes calculated between the initial dose (baseline) and the dose levels. Under a parallel group design, the traditional ANOVA type F-tests based on the two slope approaches are compared. A comparison of other tests based on the two slope approaches will also be made under a different criterion of measure of slope heterogeneity.

In the next section, model and the two slope approaches are introduced. Section 3 compares ANOVA type F-tests based on the two slope approaches. Comparison of other tests based on the two slope approaches is given in Section 4. Also included in this section are extensive simulations for evaluation of the finite sample performances of the proposed methods. In the last section, some concluding remarks are provided.

2. MODEL AND TWO SLOPES APPROACHES

Let y_{ij} be the dose response of the jth subject who receives the ith dose level d_i, $i = 1, \ldots, m+1$, $j = 1, \ldots, n$. We consider the following model

$$y_{ij} = \mu_i + d_i \epsilon_{ij}, \tag{1}$$

where μ_i is the mean dose response at the ith dose level d_i, $i = 1, \ldots, m+1$, and $d_1 < \cdots < d_{m+1}$. And ϵ_{ij} values are independent, identically distributed as a normal random variable with mean 0 and variance σ^2. Equation (1) implies that the standard deviation of dose response y_{ij} is proportional to its dose level d_i, $i = 1, \ldots, m+1$.

Define the adjacent slopes as follows

$$\theta_i = \frac{\mu_{i+1} - \mu_i}{d_{i+1} - d_i}, \quad \text{for } i = 1, \ldots, m.$$

We can then assess dose proportionality (or linearity) by testing the following hypotheses

$$H_0 : \theta_1 = \cdots = \theta_m \quad \text{vs.} \quad H_1 : H_0 \text{ is not true.} \tag{2}$$

We refer to this approach as the adjacent slope approach. Similarly, define the baseline slopes as

$$\phi_i = \frac{\mu_{i+1} - \mu_1}{d_{i+1} - d_1}, \quad \text{for } i = 1, \ldots, m.$$

We can also assess dose proportionality (or linearity) by testing the following hypotheses

$$H_0 : \phi_1 = \cdots = \phi_m \quad \text{vs.} \quad H_1 : H_0 \text{ is not true.} \tag{3}$$

This approach is referred to as the baseline slope approach.

3. *F*-TESTS BASED ON THE TWO APPROACHES

Define $\mathbf{A}$ as an $(m-1) \times m$ matrix such that $\mathbf{A}\mathbf{1}_m = 0$, where $\mathbf{1}_m$ is the m-vector of ones; then testing the null hypothesis H_0 in (2) is equivalent to testing the following null hypothesis

$$H_0 : \mathbf{A}\boldsymbol{\theta} = \mathbf{0}.$$

The parameter μ_i is estimated unbiasedly by $\hat{\mu}_i$, where

$$\hat{\mu}_i = \bar{y}_{i.} = \sum_{j=1}^{n} y_{ij}/n,$$

which is distributed as a normal random variable with mean μ_i and variance $d_i^2\sigma^2/n$. In addition, the error variance can be independently and unbiasedly estimated by

$$\hat{\sigma}^2 = \frac{1}{m+1} \sum_{i=1}^{m+1} \sum_{j=1}^{n} \frac{(y_{ij} - \bar{y}_{i.})^2}{(n-1)d_i^2}.$$

Let $\boldsymbol{\mu} = (\mu_1, \ldots, \mu_{m+1})'$ and $\mathbf{B}_1$ be the $m \times (m+1)$ matrix such that $\boldsymbol{\theta} = \mathbf{B}_1\boldsymbol{\mu}$, where

$$\mathbf{B}_1 = \begin{pmatrix} -\frac{1}{d_2-d_1} & \frac{1}{d_2-d_1} & 0 & \cdots & 0 \\ 0 & -\frac{1}{d_3-d_2} & \frac{1}{d_3-d_2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & -\frac{1}{d_{m+1}-d_m} & \frac{1}{d_{m+1}-d_m} \end{pmatrix}.$$

Then we will reject the linear hypothesis H_0 in (2) if and only if

$$T_1 = \frac{n\hat{\boldsymbol{\mu}}'\mathbf{B}_1'\mathbf{A}'(\mathbf{A}\mathbf{B}_1\mathbf{D}\mathbf{D}'\mathbf{B}_1'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_1\hat{\boldsymbol{\mu}}/(m-1)}{\hat{\sigma}^2} > F_{m-1,(m+1)(n-1),\alpha}, \tag{4}$$

where $\mathbf{D} = \mathrm{diag}\{d_1, \ldots, d_{m+1}\}$ and $F_{m-1,(m+1)(n-1),\alpha}$ is the $(1-\alpha)$th quantile of an F-distribution with $(m-1, (m+1)(n-1))$ degrees of freedom. The above F-test [Eq. (4)] is in fact a uniformly most powerful invariant (UMPI) test.

Similarly, let $\mathbf{B}_2$ be the $m \times (m+1)$ matrix such that $\phi = \mathbf{B}_2\boldsymbol{\mu}$, where

$$\mathbf{B}_2 = \begin{pmatrix} -\frac{1}{d_2-d_1} & \frac{1}{d_2-d_1} & 0 & \cdots & 0 \\ -\frac{1}{d_3-d_1} & 0 & \frac{1}{d_3-d_1} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -\frac{1}{d_{m+1}-d_1} & 0 & 0 & \cdots & \frac{1}{d_{m+1}-d_1} \end{pmatrix}.$$

Then we reject the null hypothesis H_0 in (3) if and only if

$$T_2 = \frac{n\hat{\boldsymbol{\mu}}'\mathbf{B}_2'\mathbf{A}'(\mathbf{A}\mathbf{B}_2\mathbf{D}\mathbf{D}'\mathbf{B}_2'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_2\hat{\boldsymbol{\mu}}/(m-1)}{\hat{\sigma}^2} > F_{m-1,(m+1)(n-1),\alpha}. \tag{5}$$

Although T_1 and T_2 have different expressions, it can be verified that they are actually identical. In fact, rewrite T_i as

$$T_i = \frac{n(\hat{\boldsymbol{\mu}}'\mathbf{D}^{-1})\mathbf{P}_i(\mathbf{D}^{-1}\hat{\boldsymbol{\mu}})/(m-1)}{\hat{\sigma}^2},$$

where

$$\mathbf{P}_i = \mathbf{D}\mathbf{B}_i'\mathbf{A}'(\mathbf{A}\mathbf{B}_i\mathbf{D}\mathbf{D}'\mathbf{B}_i'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_i\mathbf{D}, \quad i = 1, 2.$$

Then, 1) both $\mathbf{P}_1$ and $\mathbf{P}_2$ are projections (in the $(m+1)$-dimensional Euclidean space) onto the subspace orthogonal to the one spanned by $\mathbf{1}_{m+1}$ and $(d_1^{-1}, \ldots, d_{m+1}^{-1})'$ and 2) $(m-1)\hat{\sigma}^2 T_i/n$ is the squared distance between the origin $\mathbf{0}_{m+1}$ and the projection image of the vector $\mathbf{D}^{-1}\hat{\boldsymbol{\mu}}$ under $\mathbf{P}_i$, $T_1 = T_2$. This result implies that the two test rules [Eqs. (4) and (5)] are identical.

4. OTHER TESTS BASED ON THE TWO SLOPE APPROACHES

In the previous section, we showed that the F-tests based on the two slope approaches yield identical results. The quantity $\hat{\boldsymbol{\mu}}'\mathbf{B}_1'\mathbf{A}'(\mathbf{A}\mathbf{B}_1\mathbf{D}\mathbf{D}'\mathbf{B}_1'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_1\hat{\boldsymbol{\mu}}$ in the numerator of T_1 is to estimate $\boldsymbol{\mu}'\mathbf{B}_1'\mathbf{A}'(\mathbf{A}\mathbf{B}_1\mathbf{D}\mathbf{D}'\mathbf{B}_1'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_1\boldsymbol{\mu}$, or equivalently in terms of $\mathbf{A}\boldsymbol{\theta}$, $\boldsymbol{\theta}'\mathbf{A}'(\mathbf{A}\mathbf{B}_1\mathbf{D}\mathbf{D}'\mathbf{B}_1'\mathbf{A}')^{-1}\mathbf{A}\boldsymbol{\theta}$. Similarly, the quantity $\hat{\boldsymbol{\mu}}'\mathbf{B}_2'\mathbf{A}'(\mathbf{A}\mathbf{B}_2\mathbf{D}\mathbf{D}'\mathbf{B}_2'\mathbf{A}')^{-1}\mathbf{A}\mathbf{B}_2\hat{\boldsymbol{\mu}}$ in the numerator of T_2 is to estimate $\boldsymbol{\phi}'\mathbf{A}'(\mathbf{A}\mathbf{B}_2\mathbf{D}\mathbf{D}'\mathbf{B}_2'\mathbf{A}')\mathbf{A}\boldsymbol{\phi}$. As quadratic forms, these two quantities can be viewed as measures of the squared "generalized"

distances from the origin $\mathbf{0}$ to $\mathbf{A}\boldsymbol{\theta}$ and $\mathbf{A}\boldsymbol{\phi}$, respectively. However, we notice that these two measures are associated with different positive definite matrices, namely, $(\mathbf{AB}_1\mathbf{DD}'\mathbf{B}_1'\mathbf{A}')^{-1}$ for the former and $(\mathbf{AB}_2\mathbf{DD}'\mathbf{B}_2'\mathbf{A}')^{-1}$ for the latter.

Let $\mathbf{C}$ be an $m \times m$ symmetric, semidefinite matrix such that $\mathbf{C1}_m = 0$. Then, the two parameters $\boldsymbol{\theta}'\mathbf{C}\boldsymbol{\theta}/\sigma^2$ and $\boldsymbol{\phi}'\mathbf{C}\boldsymbol{\phi}/\sigma^2$ measure the departure from their corresponding null hypotheses based on the same measure induced by $\mathbf{C}$. For example, $\sum_{i=1}^{m}(\theta_i - \bar{\theta})^2/\sigma^2$ and $\sum_{i=1}^{m}(\phi_i - \bar{\phi})^2/\sigma^2$ correspond to $\mathbf{C} = \mathbf{I}_m - \frac{1}{m}\mathbf{U}_m$, where $\mathbf{I}_m$ is the $m \times m$ identity matrix and $\mathbf{U}_m$ is the $m \times m$ matrix of ones. It is, therefore, of interest to test the null hypothesis [Eqs. (2) and (3)] based on $\hat{\boldsymbol{\theta}}'\mathbf{C}\hat{\boldsymbol{\theta}}/\sigma^2$ and $\hat{\boldsymbol{\phi}}'\mathbf{C}\hat{\boldsymbol{\phi}}/\hat{\sigma}^2$, respectively, and compare their performances under a fixed alternative.

Define

$$T_3 = \frac{n\hat{\boldsymbol{\theta}}'\mathbf{C}\hat{\boldsymbol{\theta}}/(m-1)}{\hat{\sigma}^2} = \frac{n\hat{\boldsymbol{\mu}}'\mathbf{B}_1'\mathbf{C}\mathbf{B}_1\hat{\boldsymbol{\mu}}/(m-1)}{\hat{\sigma}^2}. \tag{6}$$

Then we reject H_0 in Eq. (2) if and only if $T_3 > c_{1,\alpha}$, where $c_{1,\alpha}$ is the $(1-\alpha)$th quantile of T_3 under H_0 in Eq. (2). It should be pointed out that under H_0, the test statistic T_3 is not F distributed because the numerator of T_3 is not chi-squared distributed, although it is independent with the denominator. Consequently, the critical value $c_{1,\alpha}$ has to be determined numerically.

Similarly, define

$$T_4 = \frac{n\hat{\boldsymbol{\phi}}'\mathbf{C}\hat{\boldsymbol{\phi}}/(m-1)}{\hat{\sigma}^2} = \frac{n\hat{\boldsymbol{\mu}}'\mathbf{B}_2'\mathbf{C}\mathbf{B}_2\hat{\boldsymbol{\mu}}/(m-1)}{\hat{\sigma}^2}. \tag{7}$$

We reject H_0 in Eq. (3) if and only if $T_4 > c_{2,\alpha}$, where $c_{2,\alpha}$ is the $(1-\alpha)$th quantile of T_4 under H_0 in Eq. (3).

It should be noted that theoretical comparison between the two non-F-tests is difficult to obtain because 1) the critical values $c_{1,\alpha}$ and $c_{2,\alpha}$ involved in the two tests have no closed form and are generally different and 2) the distributions of T_3 and T_4 under a fixed common alternative are complicated. To compare the performances of the two non-F-tests using T_3 and T_4, a simulation study was conducted to investigate the power of the two non-F-tests based on T_3 and T_4. Also included in the simulation study are the F-tests based on T_1 and T_2 described in the previous section.

In our simulation, we consider the following six dose levels $d_1 = 60\,\text{mg}$, $d_2 = 120\,\text{mg}$, $d_3 = 180\,\text{mg}$, $d_4 = 240\,\text{mg}$, $d_5 = 300\,\text{mg}$, and $d_6 = 360\,\text{mg}$. Following Cheng et al. (2006), for power calculation the mean dose response μ_i at dose d_i is generated from each of the following nonproportionality dose response patterns

$$\text{(square-root dose curve):}\quad \text{response} = 68.31\sqrt{\text{dose}} \tag{8}$$

$$\text{(2/3-th power curve):}\quad \text{response} = 25.61\ \text{dose}^{2/3} \tag{9}$$

$$\text{(quadratic dose curve):}\quad \text{response} = 0.01\ \text{dose}^2 \tag{10}$$

$$\text{(logistic dose curve):}\quad \text{response} = 1296[1 + \exp\{-(\text{dose} - 180)/35\}]^{-1} \tag{11}$$

See Fig. 1 for the plots of these patterns. Data are generated according to Eq. (1) with $\sigma = 1$. The matrix $\mathbf{C}$ in T_3 and T_4 is chosen to have the following form

$$\mathbf{C} = \begin{pmatrix} w_1 & 0 & \dots & 0 \\ 0 & w_2 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & w_m \end{pmatrix} - \begin{pmatrix} w_1^2 & w_1 w_2 & \dots & w_1 w_m \\ w_2 w_1 & w_2^2 & \dots & w_2 w_m \\ \vdots & \vdots & \ddots & \vdots \\ w_m w_1 & w_m w_2 & \dots & w_m^2 \end{pmatrix},$$

where w_i's are weights such that $w_i \geq 0$ and $\sum_{i=1}^m w_i = 1$. With the above form of matrix $\mathbf{C}$, we have

$$\boldsymbol{\theta}' \mathbf{C} \boldsymbol{\theta} = \sum_{i=1}^m w_i \left[\theta_i - \left(\sum_{j=1}^m w_j \theta_j \right) \right]^2$$

and

$$\boldsymbol{\phi}' \mathbf{C} \boldsymbol{\phi} = \sum_{i=1}^m w_i \left[\phi_i - \left(\sum_{j=1}^m w_j \phi_j \right) \right]^2.$$

Let U be a random variable having a Beta distribution with parameter (a, b) and also let

$$w_i = P\left(\frac{i-1}{m} \leq U \leq \frac{i}{m} \right), \quad i = 1, \dots, m,$$

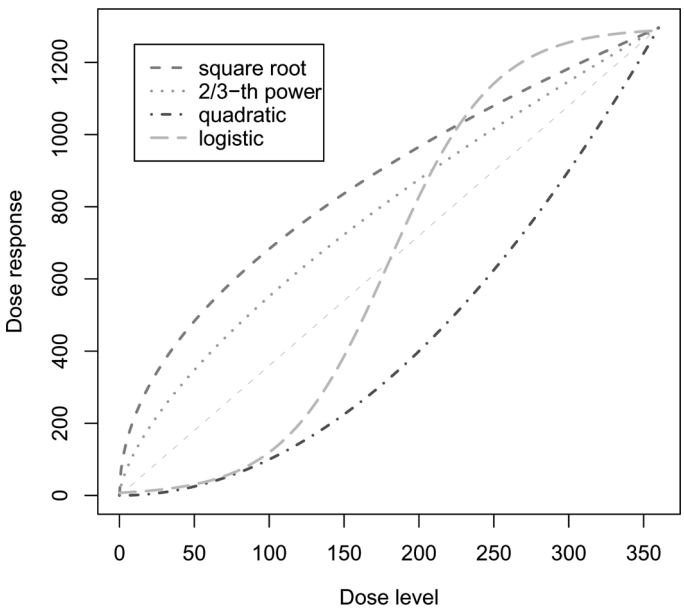

Figure 1 Some nonproportionality patterns with dose proportionality pattern superimposed (in gray).

Table 1 Estimated powers of tests based on T_1, T_3, and T_4, assuming $\sigma = 1.0$

			$\mathbf{w}(1, 1)$		$\mathbf{w}(1, 3)$		$\mathbf{w}(3, 1)$	
Pattern	n	T_1	T_3	T_4	T_3	T_4	T_3	T_4
Square-root (8)	10	0.2079	0.0640	0.2326	0.0598	0.2486	0.0968	0.1869
	20	0.3948	0.0758	0.4379	0.0633	0.4564	0.1557	0.3377
	30	0.5769	0.0933	0.6221	0.0718	0.6383	0.2337	0.4929
2/3-th power (9)	10	0.1334	0.0587	0.1532	0.0584	0.1613	0.0771	0.1239
	20	0.2377	0.0653	0.2664	0.0593	0.2857	0.1025	0.2076
	30	0.3528	0.0742	0.3818	0.0646	0.4057	0.1377	0.2895
Quadratic (10)	10	0.8435	0.2131	0.8286	0.1466	0.8954	0.4616	0.6166
	20	0.9944	0.5012	0.9929	0.2724	0.9973	0.8719	0.9321
	30	1.0000	0.7893	0.9999	0.4333	1.0000	0.9863	0.9940
Logistic (11)	10	0.9584	0.6844	0.9664	0.4245	0.9390	0.8701	0.9550
	20	0.9998	0.9811	1.0000	0.8285	0.9996	0.9978	0.9998
	30	1.0000	0.9998	1.0000	0.9774	1.0000	1.0000	1.0000

and define $\mathbf{w}(a, b) = (w_1, \ldots, w_m)'$. In our simulation, we consider three sets of weights: $\mathbf{w}(1, 1)$, $\mathbf{w}(1, 3)$, and $\mathbf{w}(3, 1)$. Note that $\mathbf{w}(1, 1)$ puts equal weight to all the dose levels while $\mathbf{w}(1, 3)$ puts heavier weights to the higher dose levels and $\mathbf{w}(3, 1)$ puts heavier weights to the lower dose levels. The estimated powers, based on 10,000 simulation runs, are presented in Table 1.

From Table 1 we learn that 1) test T_3 is uniformly inferior to either T_1 or T_4, 2) whether test T_4 is more powerful depends on the choice of weights: it could be more powerful when $\mathbf{w}(1, 3)$ is used but less powerful when weight $\mathbf{w}(3, 1)$ is used, and 3) even in the cases where T_4 is more powerful than T_1, the gain in power is not substantial.

5. CONCLUDING REMARKS

For testing dose proportionality (or linearity), various tests could be used based on either the adjacent slope approach or the baseline slope approach. We showed that the ANOVA type F-test derived in Section 3 does not depend on which slope approach was used. Although this F-test has desirable statistical properties (e.g., it is the uniformly most powerful test among all of the invariant tests), it is neither intuitive nor easy to interpret.

Tests based on T_3 and T_4, on the other hand, are very intuitive, but their statistical properties are complicated and unclear. Our simulation studies indicated that test T_3 based on the adjacent slopes may suffer substantial power loss as compared to that of test T_4 based on the baseline slopes.

The design considered in this article was a parallel group design. As a result, the slopes (rate of changes in the mean responses) were estimated from the mean dose-response curves rather than the individual dose-response profiles. When the latter is of particular interest, a different design such as an $r \times s$ crossover design with subjects receiving multiple-dose levels could be considered. It should be noted that if a sufficient length of washout period is applied to wear off the possible

carryover effect, the comparison made in this paper can be carried out similarly in a crossover design.

The comparison of the two slope approaches could also be considered for assessment of the departure from dose linearity. For example, for some prespecified constant $\delta > 0$, the following hypotheses

$$H_0 : \boldsymbol{\theta}'\mathbf{C}\boldsymbol{\theta}/\sigma^2 \geq \delta \quad \text{vs.} \quad H_1 : \boldsymbol{\theta}'\mathbf{C}\boldsymbol{\theta}/\sigma^2 < \delta \tag{12}$$

and

$$H_0 : \boldsymbol{\phi}'\mathbf{C}\boldsymbol{\phi}/\sigma^2 \geq \delta \quad \text{vs.} \quad H_1 : \boldsymbol{\phi}'\mathbf{C}\boldsymbol{\phi}/\sigma^2 < \delta \tag{13}$$

could be considered. However, a theoretical comparison is much more complicated than the one considered in Section 4. This is because that the rejection regions for testing the hypotheses in Eqs. (12) or (13) cannot be determined easily because the test statistic T_3 (or T_4) is not stochastically monotone in $\boldsymbol{\theta}'\mathbf{C}\boldsymbol{\theta}/\sigma^2$ (or $\boldsymbol{\phi}'\mathbf{C}\boldsymbol{\phi}/\sigma^2$), thus, it is unclear at which null hypothesis value of $\boldsymbol{\theta}$ (or $\boldsymbol{\phi}$) the test achieves its size. As a result, the comparison has to be made on the basis of extensive simulation studies.

REFERENCES

Cheng, B., Chow, S. C., Wang, H. (2006). Test for minor departure from dose linearity under crossover design: a slope approach (submitted).

Chow, S. C., Liu, J. P. (2003). *Design and Analysis of Clinical Trials: Concepts and Methodologies*. 2nd ed. New York: Wiley.

Law, C. G. (2000). Dose proportionality. In: Chow, S. C., ed. *Encyclopedia of Biopharmaceutical Statistics*. New York: Marcel Dekker, pp. 167–170.

Rodda, B. E., Tsianco, M. C., Bolognese, J. A., Kersten, M. K. (1988). Clinical Development. In: Peace, K. E., ed. *Biopharmaceutical Statistics for Drug Development*. New York: Marcel Dekker.

Ruberg, S. J. (1995a). Dose response studies I. Some design considerations. *J. Biopharm. Stat.* 5:1–14.

Ruberg, S. J. (1995b). Dose response studies II. Analysis and interpretation. *J. Biopharm. Stat.* 5:15–42.