BIOEQUIVALENCE:
COMPARISON OF AVERAGE VALUES WITH
GENERALIZED $p$ -VALUES

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ABSTRACT

The aim of bioequivalence studies is the evaluation of bioequivalence of pharmaceutical products. The products are usually two and basic pharmacokinetic parameters such as AUC, $C_{\text{max}}$ and $t_{\text{max}}$ are used. These studies aim at investigating the “closeness” of the distributions of the pharmacokinetic parameters (responses) for the two products, which is made mainly by comparing the average values of these responses under normality or lognormality. The existing methods of comparing average bioequivalence are based on the assumption of equal variances for the pharmacokinetic parameters. In this paper, we propose the use of generalized $p$-values, suggested by Tsui and Weerahandi in 1989, for testing average bioequivalence in the case of unequal variances. We present exact small sample size tests of average bioequivalence for parallel study designs and demonstrate how to compute their $p$-values when the pharmacokinetic responses follow normal or lognormal distribution with unequal variances.

1. INTRODUCTION

The concept of bioavailability and bioequivalence plays an important role in pharmaceutical research and development, especially in the generic drug industry. For this reason, in the last thirty years, studies of bioavailability whose purpose is the evaluation of bioequivalence of two or more products, have become very popular in the drug industry. Since the early ’70s a large and constantly increasing bibliography on statistical methods for bioequivalence studies has appeared. The statistical aspects of these studies are based on the concept of the “closeness” between the marginal distributions of the products’ pharmacokinetic responses. Usually the products are two: the test product T and the reference product R. Based on the fact in many cases that the distribution of a random variable can be
determined by its moments, the closeness between the two distributions can be evaluated from the two first moments of the two products’ marginal distributions.

In this paper, we will deal with the comparison of the first moments, i.e. the means of the distributions of the pharmacokinetic parameters of the two products. The studies based on the means are mentioned in the bibliography as average bioequivalence studies. Regulations of most countries including Greece (ΕΟF 1996), the other European Union countries (EMEA 2002,2003), the United States of America (FDA) and Japan require only evidence for average bioequivalence in order to give approval for generics. So we will consider two products as bioequivalent, if the average values of the pharmacokinetic parameters for the two drugs e.g. AUC, C_{max}, T_{max}, are close enough. According to the FDA regulations, if we define by μ_{T} the population mean of one pharmacokinetic parameter, e.g. AUC, of the test product T and by μ_{R} the population mean of AUC for the reference product R, in order to prove the bioequivalence, we must test the hypothesis:

\[ H_0 : \frac{\mu_T}{\mu_R} \leq \delta_L \quad \text{versus} \quad H_\alpha : \frac{\mu_T}{\mu_R} \geq \delta_U \]

where \( \delta_U \) and \( \delta_L \) are given known constants. The European Union and the FDA use \( \delta_U = 1.25 \) and \( \delta_L = 0.80 = 1/1.25 \) and test this hypothesis at a 95\% confidence level.

It has been observed that the pharmacokinetic parameters usually follow a normal or lognormal distribution. For this reason, the statistical methodologies for testing bioequivalence of two products are based on comparing the mean values of two normal or lognormal distributions. Another important assumption which is regularly employed is that the variances of the pharmacokinetic parameter for the two products are equal. Under this assumption, Berger and Hsu (1996) and Chow and Liu (1992) produce exact tests for testing bioequivalence of two products. In the case of unequal ranges between the results of two products, the methods that are used do not give exact results [Chow and Liu (1992), p. 161-185]. In this paper we present exact small sample size tests for the comparison of average bioequivalence in the case of unequal variances. The tests are based on the concept of generalized p-values, which was introduced by Tsui and Weerahandi in 1989. The method of generalized p-values is briefly presented in Section 2 with an application to the Behrens-Fisher problem. In Section 3 we present two one-sided bioequivalence tests based on generalized p-values under the assumption of unequal variances for two distributional cases: normality and lognormality and under parallel, i.e. independent, designs. Similar results have
been obtained for cross-over designs and will be presented elsewhere. For statistical issues related with bioequivalence studies see Papaioannou (2002).

2 GENERALIZED p – VALUES

2.1 General theory. The concept of generalized p-values was presented by Tsui and Weerahandi in 1989 in connection with problems of significant testing for one-sided hypotheses of the form \( H_0 : \theta \leq \theta_0 \) versus \( H_\alpha : \theta > \theta_0 \) or of the form \( H_0 : \theta \geq \theta_0 \) versus \( H_\alpha : \theta < \theta_0 \), where \( \theta \) is the scalar parameter of our interest, and there appears a nuisance parameter \( \eta \).

Let \( X \) be a random variable, with density function \( f(x|\xi) \) where \( \xi = (\theta, \eta) \) is an unknown vector of parameters involving \( \theta \), the parameter of our interest and \( \eta \), the vector of nuisance parameters. Let \( X \) be the sample vector and \( x \) the observed values of \( X \). Our problem is to test the null hypothesis \( H_0 : \theta \leq \theta_0 \) (or \( H_0 : \theta \geq \theta_0 \)). For this purpose we usually employ tests of size \( \alpha \), namely tests with constant significance level \( \alpha \). In testing problems which include nuisance parameters sometimes it is difficult or impossible to find such tests. In these cases, the researcher is satisfied with a level \( \alpha \) test, namely a test with power function so that \( \sup_{\theta \in H_0} \beta(\theta) \leq \alpha \). Though this procedure seems to be more flexible than the fixed level testing, there appear difficulties in multiparameter problems. One such a problem is, when the p-value depends on \( \eta \), the vector of nuisance parameters so it might be difficult to estimate it.

In order to surpass these difficulties, we consider a generalized test function of the form \( T(X;x,\xi) \), which is not only a function of \( X \) but also involves the observed \( x \) and the parameter \( \xi \). We demand from this generalized test statistic to satisfy the following three requirements:

1. \( t_{\text{obs}} = T(x;x,\xi) \) to be free of \( \xi \).
2. for fixed \( x \) and \( \xi \) the distribution of \( T(X;x,\xi) \) to be free of the nuisance parameter \( \eta \) and to be a function of a known distribution.
3. for fixed \( x \) and \( \eta \), \( T(X;x,\xi) \) must be a stochastically monotone function of \( \theta \).

The quantity \( T(X;x,\xi) \) plays the role of a test statistic, which, however, depends on the observed value \( x \) and the parameters \( \theta \) and \( \eta \). \( t_{\text{obs}} \), which is \( T(x;x,\xi) \), may depend on \( \theta \) but at \( \theta_0 \) of \( H_0 \) it has a known value as is the case with tests of significance. A generalized test statistic \( T(X;x,\xi) \) which satisfies the previous requirements and in particular is stochastically increasing in \( \theta \) leads to the following generalized extreme or rejection region:

\[
C_x(\xi) = \{X : T(X;x,\xi) - T(x;x,\xi) \geq 0\} = \{X : T(X;x,\xi) \geq t_{\text{obs}}\}
\]

for testing \( H_0 : \theta \leq \theta_0 \).
If the generalized test statistic \( T(X;x,\xi) \) is stochastically decreasing in \( \theta \), we consider the test based on the generalized extreme or rejection region:

\[
C_{\xi}(\xi) = \{ X : T(X;x,\xi) - T(x;x,\xi) \leq 0 \} = \{ X : T(X;x,\xi) \leq t_{\text{obs}} \}
\]

So, following the usual definition for the p-value, the p-value for this test is:

\[
p(x) = \sup_{\theta \in H_0} \Pr(X \in C_{\xi}(\xi) | \theta).
\]

If the p-value is smaller than \( \alpha \), we will reject \( H_0 \), as usual. Requirement 3 guarantees that the test that we produce based on the statistic \( T(X;x,\xi) \) is the uniformly most powerful (UMP) level \( \alpha \) test, if this statistic is sufficient, since it is known that for the existence of a UMP test of level \( \alpha \) of \( H_0 : \theta \leq \theta_0 \) against \( H_1 : \theta > \theta_0 \), there must be a sufficient statistic \( T(X) \) for \( \theta \) and the family of pdfs or pmfs of \( T \) to have monotone likelihood ratio. According to Lehmann (1986), this means that \( T(X) \) should be a stochastically monotone function of \( \theta \). Moreover, Requirement 3 means that the probability \( \Pr(T(X;x,\xi) \geq t) \) increases as \( \theta - \theta_0 \) increases if \( T(.) \) is stochastically increasing, whereas it decreases as \( \theta - \theta_0 \) increases if \( T(.) \) is stochastically decreasing in \( \theta \). So we have respectively:

\[
p(x) = \sup_{\theta \in H_0} \Pr(T(X;x,\theta, \eta) \geq t) = \Pr(T(X;x,\theta_0, \eta) \geq t)
\]

\[
p(x) = \sup_{\theta \in H_0} \Pr(T(X;x,\theta, \eta) \leq t) = \Pr(T(X;x,\theta_0, \eta) \leq t).
\]

So it is possible to evaluate these p-values since they are independent from the nuisance parameter.

2.2 Application of generalized p-values: The Behrens-Fisher problem. In order to demonstrate the possible use of the generalized p-values procedure, we consider the Behrens–Fisher problem, which can be formulated as follows. Let \( X_1, X_2, \ldots, X_{n_1} \) and \( Y_1, Y_2, \ldots, Y_{n_2} \) be two sets of independent observations from the normal populations \( N(\mu_1, \sigma_1^2) \) and \( N(\mu_2, \sigma_2^2) \) respectively. We also assume that \( X_1, X_2, \ldots, X_{n_1} \) and \( Y_1, Y_2, \ldots, Y_{n_2} \) are independent. We wish to test the null hypothesis \( H_0: \mu_1 - \mu_2 \leq 0 \) versus the alternative \( H_1: \mu_1 - \mu_2 > 0 \) based on the independent sufficient statistics \( \overline{X}, \overline{Y}, S_1^2 \) and \( S_2^2 \), which are or are related to the maximum likelihood estimators of the means \( \mu_1 \) and \( \mu_2 \) and the variances \( \sigma_1^2 \) and \( \sigma_2^2 \) respectively. In this problem we are interested in the parameter \( \theta = \mu_1 - \mu_2 \) and the nuisance parameter is \( \eta = (\sigma_1^2, \sigma_2^2) \). So, following Tsui and Weerahandi (1989) and Weerahandi (1995) the random quantity which can be used as a generalized test statistic to find the extreme region \( C_{x,y}(\xi) \) for the Behrens–Fisher problem and which complies with the requirements (2.1) is:
\[ T(X,Y; x, y, \eta) = (\bar{X} - \bar{Y} - \theta) \left( \frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2} \right)^{1/2} \left( \frac{\sigma_1^2 S_2^2}{n_1 S_1^2} + \frac{\sigma_2^2 S_1^2}{n_2 S_2^2} \right)^{1/2} \]  

(2.2)

This can be expressed as follows:

\[
T = Z \left[ \frac{s_1^2}{U} + \frac{s_2^2}{V} \right]^{1/2} \quad \text{or} \quad T = \frac{Z}{(U + V)^{1/2}} \left[ \frac{s_1^2}{U} + \frac{s_2^2}{V} \right]^{1/2},
\]

(2.3)

where \( Z \sim N(0,1) \), \( U \sim X_{n_1-1}^2 \) and \( V \sim X_{n_2-1}^2 \), and \( Z, U \) and \( V \) are independent. Note that the random quantity \( T \) has the same distribution with \( Z \left( \frac{s_1^2}{U} + \frac{s_2^2}{V} \right)^{1/2} \) and \( T(x, y; x, y, \eta) = \bar{x} - \bar{y} - \theta \).

We see that the family of distributions of \( T(X,Y; x, y, \eta) \) for fixed \( x \) and \( y \) is stochastically increasing in \( \theta \) and as a result we have the generalized extreme region:

\[ C_{x,y}(\theta, \eta) = \{(X,Y) : T(X,Y; x, y, \eta) - T(x, y; x, y, \eta) \geq 0\} \]

According to this extreme region we can compute a p-value, which will not depend on the nuisance parameter. For the Behrens – Fisher problem the generalized p-value is:

\[
p(\chi) = Pr(T \geq t_{obs} \bigg| \theta = 0) = Pr(T \geq \bar{x} - \bar{y} - \theta \bigg| \theta = 0)
\]

\[
= Pr \left[ T \cdot (n_1 + n_2 - 2)^{1/2} \left( \frac{s_1^2}{B} + \frac{s_2^2}{I - B} \right)^{1/2} \geq \bar{x} - \bar{y} \right] = E_B \left\{ G_{n_1 + n_2 - 2} \left( \frac{n_1 + n_2 - 2}{s_1^2 + s_2^2} \right)^{1/2} \right\},
\]

where \( T = Z[(U + V)/(n_1 + n_2 - 2)]^{1/2} \) which follows Student’s t distribution with \( (n_1 + n_2 - 2) \) d.f. and is independent from \( B = U/(U + V) \) which follows Beta with parameters \( (n_1 - 1)/2 \) and \( (n_2 - 1)/2 \). \( G_{n_1 + n_2 - 2} \) is the p.d.f. of Student’s t distribution with \( (n_1 + n_2 - 2) \) d.f. and where \( E_B \) denotes expectation with respect to \( B \).

The generalized p-value is computed using the first expression of \( T \) in (2.3) by generating random values from the r.v.’s \( Z, U \) and \( V \) (Monte Carlo). For details see Poulopoulou, S (2004).

### 3. BIOEQUIVALENCE TEST IN CASE OF UNEQUAL VARIANCES, \( \sigma_1^2 \neq \sigma_R^2 \).

Using the previous method of generalized p-values, we can produce exact tests for testing the bioequivalence of two products when the pharmacokinetic responses of the two products have unequal variances. In this section \( X \) and \( Y \) will denote any of the pharmacokinetic parameters mentioned in Section 1.
3.1 NORMALITY ASSUMPTION.

Let \( X_1, X_2, \ldots, X_n \) be a random sample of a normal population with mean \( \mu_T \) and variance \( \sigma^2_T \), and let \( Y_1, Y_2, \ldots, Y_n \) be an independent random sample from a normal population with mean \( \mu_R \) and variance \( \sigma^2_R \). The bioequivalence assumption (1) can be transformed to \( H_{\alpha 1}^*: \delta_1 \leq 0 \) versus \( H_{\alpha 1}^*: \delta_1 > 0 \) and \( H_{\alpha 2}^*: \delta_2 < 0 \), where \( \delta_1 = \mu_T - \delta L \mu_R \) and \( \delta_2 = \mu_T - \delta U \mu_R \) so we can handle this problem as oneBehrens – Fisher pseudo problem. Based on the fact that \( \bar{X} - \delta L \bar{Y} \sim N(\delta_1, \sigma^2_T / n_1 + \delta L^2 \sigma^2_R / n_2) \), which depends on the parameter \( \delta_1 \) of our interest and the nuisance parameter \( \sigma^2_T / n_1 + \delta L^2 \sigma^2_R / n_2 \) and \( \bar{X} - \delta U \bar{Y} \sim N(\delta_2, \sigma^2_T / n_1 + \delta U^2 \sigma^2_R / n_2) \), which depends on parameter \( \delta_2 \) of our interest and the nuisance parameter \( \sigma^2_T / n_1 + \delta U^2 \sigma^2_R / n_2 \) and in view of (2.2) we can consider the following random quantities, as generalized random quantities for testing the bioequivalence assumption:

\[
T_1(X,Y; x, y, \mu_T, \mu_R, \sigma^2_T, \sigma^2_R) = \frac{\sqrt{\frac{\sigma^2_T}{n_1} + \delta L^2 \sigma^2_R / n_2}}{\left(\frac{\sigma^2_T}{n_1} + \delta L^2 \sigma^2_R / n_2\right)} \cdot \frac{\bar{X} - \delta L \bar{Y} - \delta_1}{\sqrt{\sigma^2_T / n_1 + \delta L^2 \sigma^2_R / n_2}} \quad (3.1)
\]

\[
T_2(X,Y; x, y, \mu_T, \mu_R, \sigma^2_T, \sigma^2_R) = \frac{\sqrt{\frac{\sigma^2_T}{n_1} + \delta U^2 \sigma^2_R / n_2}}{\left(\frac{\sigma^2_T}{n_1} + \delta U^2 \sigma^2_R / n_2\right)} \cdot \frac{\bar{X} - \delta U \bar{Y} - \delta_2}{\sqrt{\sigma^2_T / n_1 + \delta U^2 \sigma^2_R / n_2}} \quad (3.1)
\]

These statistics can be expressed as follows:

\[
T_1 \sim Z\left(s^2_T / U + \delta L^2 s^2_R / V\right)^{1/2} + \delta_1 \quad \text{and} \quad T_2 \sim Z\left(s^2_T / U + \delta U^2 s^2_R / V\right)^{1/2} + \delta_2 , \quad (3.2)
\]

where \( Z \sim N(0, 1) \), \( U = \frac{n_1 S^2_T}{\sigma^2_T} \sim X^2_{n_1-1} \) and \( V = \frac{n_2 S^2_R}{\sigma^2_R} \sim X^2_{n_2-1} \) and the random variables \( Z \), \( U \) and \( V \) are independent. Since \( T_1 \) and \( T_2 \) are stochastically increasing in \( \delta_1 \) and \( \delta_2 \) respectively, the generalized p-value for testing the left-hand sided null hypothesis of form \( H_{\alpha 1}^*: \delta_1 \leq 0 \) versus \( H_{\alpha 1}^*: \delta_1 > 0 \) is:

\[
p(x) = Pr(T_1 \geq t_{1,obs} | \delta_1 = 0) = Pr\left[T_1 \cdot (n_1 + n_2 - 2)^{-1/2} \left(s^2_T / B + \delta L^2 s^2_R / I - B\right)^{1/2} \geq \bar{X} - \delta L \bar{Y}\right],
\]

and the generalized p-value for testing the right-hand sided null hypothesis of the form \( H_{\alpha 2}^*: \delta_2 \geq 0 \) versus \( H_{\alpha 2}^*: \delta_2 < 0 \) is:
\[ p(x) = Pr(T_1 \leq t_{\text{obs}}, \delta_1 = 0) = Pr\left[ T_1, (n_1 + n_2 - 2)^{-1/2} \left( \frac{s_1^2}{B} + \delta_2^2 \right) \frac{s_2^2}{1 - B} \right]^{1/2} \leq \bar{x} - \delta_0 y \]

where \( B = U/(U + V) \), \( T_1 = T_2 = \frac{Z}{(U + V)/(n_1 + n_2 - 2)} \) when \( \delta_1 = 0 \) and \( \delta_2 = 0 \). In this case \( T_1 \) and \( T_2 \) follow the Student’s t distribution with \( n_1 + n_2 - 2 \) d.f. and are independent of \( B \), which follows Beta with parameters \((n_1 - 1)/2\) and \((n_2 - 1)/2\). The p-value can be computed by Monte Carlo using (3.2). For details see Poulopoulou (2004). In analogy with the TOST test the previous test of the bioequivalence assumption can be called \( \text{“Two one sided generalized p – value tests”} \) (TOSGPVT).

3.2 Lognormality assumption. Let our data follow lognormal distributions with unequal parameters. More specifically let \( X_1 \) be the lognormal quantity associated with observations from the Test drug and suppose \( X_1 \) is a lognormal random variable with parameters \( \eta_T \) and \( \sigma^2_T \). Let also \( Y_1 = \ln(X_1) \). Similarly let \( X_2 \) be the lognormal quantity for the Reference drug with parameters \( \eta_R \) and \( \sigma^2_R \) and \( Y_2 = \ln(X_2) \). The means for the test and the reference products are: \( \mu_T = \exp(\eta_T + \sigma^2_T / 2) \) and \( \mu_R = \exp(\eta_R + \sigma^2_R / 2) \) respectively. So the bioequivalence assumption becomes:

\[ \delta_L \leq \frac{\mu_T}{\mu_R} = \exp[\eta_T + \sigma^2_T / 2 - (\eta_R + \sigma^2_R / 2)] \leq \delta_U \]

which is equivalent to: \( \theta_L \leq \eta_T + \sigma^2_T / 2 - (\eta_R + \sigma^2_R / 2) \leq \theta_U \), where \( \theta_L = \ln(\delta_L) \) and \( \theta_U = \ln(\delta_U) \). So the assumption that must be tested, setting \( \theta_T = \eta_T + \sigma^2_T / 2 \) and \( \theta_R = \eta_R + \sigma^2_R / 2 \), in the case of the lognormal model with unequal variances can be separated to two one-side bioequivalence hypothesis: \( H_{a1} : \theta_T - \theta_R \leq \theta_L \) versus \( H_{a1} : \theta_T - \theta_R > \theta_L \) and \( H_{a2} : \theta_T - \theta_R \geq \theta_L \) versus \( H_{a2} : \theta_T - \theta_R < \theta_U \).

Based on the fact that \( Y_1 \sim N(\eta_T, \sigma^2_T) \), which depends on the parameter \( \eta_T \) of our interest and the nuisance parameter \( \sigma^2_T \) and that \( Y_2 \sim N(\eta_R, \sigma^2_R) \), which depends on the parameter \( \eta_R \) of our interest and the nuisance parameter \( \sigma^2_R \), then we can consider the generalized random quantities:

\[
T_1(Y_1; y_1, \mu_T, \sigma^2_T) = \frac{\bar{Y}_1 - \eta_T}{S_T/\sqrt{n_1}} + 1 \frac{\sigma^2}{S_T^2} \frac{s_T^2}{\sqrt{n_1}} + \frac{Z_T}{U/\sqrt{n_1 - 1}} \frac{s_T}{\sqrt{n_1}} + 1 \frac{1}{2} \frac{s_T^2}{(n_1 - 1)}
\]

\[
T_2(Y_2; y_2, \mu_R, \sigma^2_R) = \frac{\bar{Y}_2 - \eta_R}{S_R/\sqrt{n_2}} + 1 \frac{\sigma^2}{S_R^2} \frac{s_R^2}{\sqrt{n_2}} + \frac{Z_R}{V/\sqrt{n_2 - 1}} \frac{s_R}{\sqrt{n_2}} + 1 \frac{1}{2} \frac{s_R^2}{(n_2 - 1)}
\]
where \( Z^T = \sqrt{n_1} (\bar{Y}_1 - \eta_Y) \sigma_T \sim N(0,1), \ Z^R = \sqrt{n_2} (\bar{Y}_2 - \eta_R) \sigma_R \sim N(0,1), \ U^2 = (n_1 - 1) \)

\( S^2_T / \sigma^2_T \sim \chi^2_{n_1-1} \) and \( V^2 = (n_2 - 1) S^2_R / \sigma^2_R \sim \chi^2_{n_2-1} \), which are also independent. So for testing the null hypotheses \( H_01 \) and \( H_02 \) we define the generalized random quantities:

\[
T_L = T_1 - T_2 - (\theta_T - \theta_R) + \theta_L \quad \text{and} \quad T_U = T_1 - T_2 - (\theta_T - \theta_R) + \theta_U
\]

Under bioequivalence the distribution of \( T_L \) and \( T_U \) are given by:

\[
T_L \sim \frac{Z^T}{U/\sqrt{n_1-1}} - \frac{1}{2} \frac{s^2_T}{U^2/(n_1-1)} - \frac{Z^R}{V/\sqrt{n_2-1}} - \frac{s^2_R}{V^2/(n_2-1)} - (\theta_T - \theta_R) + \theta_L,
\]

\[
T_U \sim \frac{Z^T}{U/\sqrt{n_1-1}} - \frac{1}{2} \frac{s^2_T}{U^2/(n_1-1)} - \frac{Z^R}{V/\sqrt{n_2-1}} - \frac{s^2_R}{V^2/(n_2-1)} - (\theta_T - \theta_R) + \theta_U.
\]

The quantities \( T_L \) and \( T_U \) have observed values free of nuisance parameters.

\[
T_{Lobs} = T_{1obs} - T_{2obs} - (\theta_T - \theta_R) + \theta_L = \theta_T - \theta_R - (\theta_T - \theta_R) + \theta_L = \theta_L
\]

\[
\text{and} \quad T_{Uobs} = T_{1obs} - T_{2obs} - (\theta_T - \theta_R) + \theta_U = \theta_T - \theta_R - (\theta_T - \theta_R) + \theta_U = \theta_U.
\]

We also observe that \( T_L \) and \( T_U \) stochastically decreasing with \( \theta_T - \theta_R \). Therefore the generalized p-value for testing \( H_01 \) is given by:

\[
p(x) = Pr(T_L \leq \theta_L | \theta_T - \theta_R = \theta_L)
\]

whereas for testing \( H_02 \) we have the generalized p-value:

\[
p(x) = Pr(T_U \geq \theta_U | \theta_T - \theta_R = \theta_U)
\]

The p-value can be computed by Monte Carlo using (3.3). For details see Pouloulopoulo (2004). See also Krishnamoorthy and Mathew (2003).

**ΠΕΡΙΛΗΨΗ**

Ο σκοπός των μελετών βιοισοδυναμίας είναι η αποτίμηση της βιοισοδυναμίας δύο προϊόντων, όπου για την αποτίμηση αυτή χρησιμοποιούνται βασικοί φαρμακευτικοί παράμετροι όπως AUC, C_{\text{max}} και t_{\text{max}}. Στόχος των μελετών αυτών είναι η διερεύνηση της “ισοδυναμίας” των περιθώριων κατανομών των φαρμακοκινητικών αποκρισιών για τα δύο προϊόντα, η οποία πραγματοποιείται κυρίως µε την σύγκριση των μέσων τιµών των φαρμακοκινητικών αποκρισιών κάτω από την υπόθεση της κανονικότητας ή της λογαριθµοκανονικότητας. Αρκετοί µέθοδοι έχουν προταθεί για την αποτίμηση της μέσης βιοισοδυναμίας, οι οποίες βασίζονται στην σύγκριση των μέσων τιµών των φαρμακοκινητικών παραµέτρων κάτω από την υπόθεση ίσων διακυµάνσεων των φαρμακοκινητικών παραµέτρων των δυο προϊόντων. Σε αυτήν την εργασία προτείνουμε την εφαρµογή της ιδέας των γενικευµένων p-values, που προτάθηκε από τους Tsui και Weerahandi το 1989, σε προβλήµατα ελέγχου µέσης βιοισοδυναμίας για την παραγωγή ελέγχων σύγκρισης της µέσης βιοδιαθεσιµότητας στην περίπτωση άνισων διακυµάνσεων. Ειδικότερα παρουσιάζουµε ακριβείς ελέγχους µικρών δειγµάτων της µέσης βιοισοδυναμίας για παράλληλους σχεδιασµούς μελετών βιοισοδυναμίας, στις περιπτώσεις που οι φαρμακοκινητικές αποκρισίες ακολουθούν κανονική ή λογαριθµοκανονική κατανομή με άνισες διακυµάνσεις.
REFERENCES


