AN UNBIASED TEST FOR THE BIOEQUIVALENCE PROBLEM

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ABSTRACT. It is shown that the standard two one–sided tests procedure for bioequivalence is a biased test. Better tests exist. In this paper, an unbiased α–level test and other tests which are uniformly more powerful than the two one–sided tests procedure are constructed. Its power can be noticeably larger than that of the α–level two one–sided tests procedure.

1. Introduction.

Recently there has been great interest in the problem of demonstrating bioequivalence of treatments, especially in the pharmaceutical industry. One of the reasons is that developing a marketable drug which is bioequivalent (i.e., equivalent in efficacy) to a well established drug typically costs 1% or less relative to the cost of developing a new one.

The statistical formulation of the problem is by now agreed upon to be the following hypothesis testing problem. Let m_1 and m_2 be the parameters corresponding to the two treatments. For example, the parameter of interest may be one of the pharmacokinetic parameters (AUC, $C_{\max}$ or $T_{\max}$) of the concentration–time curves.

Bioequivalence of the two treatments is defined as $\Delta_1 \leq \rho \leq \Delta_2$ where $\rho = m_1/m_2$ and Δ_i, $i = 1, 2$, is the tolerance limit prespecified by a regulatory agency. The statistical problem is then to test

$$H_0 : \rho > \Delta_2 \text{ or } \rho < \Delta_1 \quad \text{versus} \quad H_1 : \Delta_1 \leq \rho \leq \Delta_2.$$

If one can reject H_0, then one can declare bioequivalence. In the American FDA (1992) guidance, $\Delta_1 = .8$ and $\Delta_2 = 1.25$.

It is also recommended in the same guidance that a logarithmic transformation be applied and hence the ratio problem is turned into a difference problem, i.e.,

$$\theta = \ln(\rho) = \mu_1 - \mu_2$$

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where $\mu_i = \log m_i$. The hypotheses become

$$H_0 : |\theta| > \Delta \quad \text{versus} \quad H_1 : |\theta| < \Delta, \tag{1.1}$$

where $\Delta = \log 1.25$ in the FDA's guidance. Note in this special case, the transformation leads to a symmetric interval of θ. In general even if an asymmetric interval is obtained, one can make a simple location transformation to turn it into a symmetric interval. Therefore symmetry in (1.1) can be assumed without loss of generality.

The standard test as required in the FDA guidance (1992) is the two one–sided tests procedure. To describe this test, let D be an estimate of θ with

$$D \sim N(\theta, \sigma^2) \tag{1.2}$$

and S^2 be an independent observation such that

$$S^2/\sigma^2 \sim \text{ chi squared distribution with } v \text{ degrees of freedom.} \tag{1.3}$$

The simplest special case involves a two sample problem with observations

$$X_1 \cdots X_m \overset{i.i.d.}{\sim} N(\mu_1, \sigma_0^2) \quad \text{and} \quad Y_1 \cdots Y_n \overset{i.i.d.}{\sim} N(\mu_2, \sigma_0^2)$$

where for example these are the independent observations corresponding to two different treatments. Let $D = \overline{X} - \overline{Y}$ and $S^2 = \left(\frac{1}{m} + \frac{1}{n}\right)\left(\sum(X_i - \overline{X})^2 + \sum(Y_i - \overline{Y})^2\right)$ reducing to the above setting with $\sigma^2 = \left(\frac{1}{m} + \frac{1}{n}\right)\sigma_0^2$ and $v = m + n - 2$. The general linear model, including the cross over design or more generally ANOVA, can be reduced to (1.2) and (1.3) as well.

The α level two one–sided tests procedure proposed in Schuirmann (1987) corresponds to the rejection region C_2 which consists of D and S such that

$$\Delta \geq |D| + t_\alpha \frac{S}{\sqrt{v}}, \tag{1.4}$$

where t_α is the upper α quantile of a t distribution with v degrees of freedom. (A related but more general type of test has been proposed in Berger (1982).) The two one–sided tests procedure is, however, biased. In fact even for $\theta = 0$, it can be seen that the power function satisfies

$$\lim_{\sigma \to \infty} P(C_2) = 0.$$

Several attempts have been made to improve upon the two one–sided tests procedure. See, for example, Anderson and Hauck (1983), and Rocke (1984 and 1985). These alternative tests, however, are only approximately α–level. Existence of a better test with exact level α was established in Hwang and Liu (1992). Munk (1993) constructed a test which is shown numerically to be α–level ($\alpha = .1$) for degrees of freedom larger than 10 and which is uniformly more powerful than the two one–sided test procedure.

In this paper we construct an unbiased α–level test. In the construction, it is seen that the rejection region of the unbiased test always contains properly the rejection region (1.4). Therefore the unbiased test is uniformly more powerful than the α–level two one–sided tests procedure. See Theorem 1. The improvement in power may be quite noticeable.