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Current and future Statistical Consideration in Bioequivalence Trials

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Abstract

In 2001 US FDA proposed a draft guidance for future in vivo bioequivalence studies. The guidance suggested specific criteria for new drug sponsors to show prescribability and switchability in bioequivalence testing for approval of generic drugs. However, there is less acceptance of the need to change statistical procedures and study designs from those currently used to assess the current criterion of average bioequivalence. The measures of population and individual bioequivalence testing are introduced and statistical procedures for them are discussed.

Keywords : Bioequivalence, Crossover design, Population and Individual BE, Prescribability and Switchability

1. Introduction

In 1997 the United States Food and Drug Administration (US FDA) issued its first draft guidance for industry on average, population, and individual approaches to establish bioequivalence; this was updated in 1999 and 2001. In this draft guidance, US FDA recommends that average bioequivalence be replaced by two new approaches, termed population bioequivalence and individual bioequivalence. These new approaches were motivated by the fact that average bioequivalence (ABE) deals only with the comparison of population means and nor with that of the variances of the respective bioequivalence metric. Moreover, the ABE criterion does not assess subject-by-formulation interaction, that is, the variation in the average test and reference difference among individuals.

The US FDA draft guidance and the proposed concepts have been subjected to intensive discussions. The trade-off granted for the mean differences in cases of a reduced variance for the test formulation caused

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major concerns by academia and the pharmaceutical industry. From a statistical perspective, criticism has focused on the aggregate criteria on the logarithmic scale, which have no interpretation in natural parameter space, and the loss of the consistency of the bioequivalence decision, which means that individual bioequivalence (IBE) should imply population bioequivalence (PBE), which, in turn, should imply ABE.

Currently the Korea FDA does not adopt the US FDA guidance, but they are considering them now since many countries' FDAs included Japan, EC etc. already recommended them. In this paper, we discuss the current statistical issues of newly recognized bioequivalence trial and this leads to help establishing the new criterions of the bioequivalence trial in Korea.

2. Statistical Model

Consider 2x2m replicated crossover design, in each sequence, each subject receives the test formulations m times and the reference formulations m times at different dosing periods. When m=1, 2x2m replicated crossover design reduces to the standard two-sequence two-period 2x2 crossover design. On the other hand, when m=2, the 2x2m replicated crossover design becomes a 2x4 crossover design, which is recommended by the US FDA for assessment of population/individual bioequivalence.

Suppose that n_1 subjects are assigned to the first sequence and n_2 subjects are assigned to the second sequence. Let y_{ijkl} be the pharmacokinetic observation such as AUC or CMAX from jth subject($j = 1, \cdots, n_i$) in the ith sequence($i = 1, 2$) under the lth replicate($l = 1, \cdots, m$) of the kth treatment ($k = T, R$). The following mixed effects model(Chinchilli and Esinhart, 1996) can be considered to describe 2x2m replicated crossover design :

$$y_{ijkl} = \mu_k + \gamma_{ikl} + S_{ijk} + \epsilon_{ijkl} \quad (1)$$

where μ_k is the treatment effect for formulation k, γ_{ikl} is the fixed effect of the lth replicate on the treatment k in the ith sequence with constraint $\sum_{i}^{2}\sum_{l}^{m}\gamma_{ikl} = 0$, (S_{ijT}, S_{ijR}) are the random effects of the jth subjects in the ith sequence, which are independent and identically distributed as a bivariate

normal random vector with mean $(0, 0)'$ and covariance matrix

$$\Sigma_B = \begin{pmatrix} \sigma_{BT}^2 & \rho\sigma_{BT}\sigma_{BR} \\ \rho\sigma_{BT}\sigma_{BR} & \sigma_{BR}^2 \end{pmatrix}.$$

Note that σ_{BT}^2 and σ_{BR}^2 are intersubject variances under the test formulation and the reference formulation, respectively. ϵ_{ijkl}s are independent random variables from the normal distribution with mean 0 and variance σ_{WT}^2 or σ_{WR}^2, which are intrasubject variances under the test formulation and the reference formulation, respectively. It is assumed that (S_{ijT}, S_{ijR}) and ϵ_{ijkl} are independent.

3. Population and Individual Bioequivalence

One can evaluate bioequivalence from a viewpoint of quality assurance for generic drug products. Difference in population averages, $\mu_T - \mu_R$, difference in population intrasubject variability $\sigma_{WT}^2 - \sigma_{WR}^2$ and subject-by-formulation interaction σ_D^2 can be considered as three characteristics representing the quality assurance for the generic drug product,

$$\text{where } \sigma_D^2 = (\sigma_{BT} - \sigma_{BR})^2 + 2(1-\rho)\sigma_{BT}\sigma_{BR}.$$

As a result, criteria for evaluation of either population or individual bioequivalence are functions of these parameters. For example, the criterion for ABE adopted by most regulatory agencies is formulated on the logarithmic scale for some pharmacokinetic measures

$$-\theta < \mu_T - \mu_R < \theta \text{ or } (\mu_T - \mu_R)^2 < \theta_0.$$

On the other hand, the intrasubject variability can be formulated

$$\sigma_{WT}^2 - \sigma_{WR}^2 < \theta_1,$$

where θ_1 is the allowable upper limit for the test intrasubject variability over the reference intrasubject variability.

In addition, a possible criterion for subject-by-formulation interaction can also be formulated in terms of its variance as

$$\sigma_D^2 < \theta_2,$$

where θ_2 is the allowable upper limit of subject-by-formulation interaction.

Bioequivalence can be claimed if each of three criteria are met. Because this approach first evaluates differences in averages, intrasubject variability, and variance of subject-by-formulation interaction separately, it is referred as to the disaggregate criterion. If the criterion is a single summary measure composed of $(\mu_T-\mu_R)^2$, $(\sigma^2_{WT}-\sigma^2_{WR})$, and σ^2_D, it is called the aggregate criterion.

Let us denote by y_R and y_R' the responses on two randomly selected subjects receiving the reference drug and by y_T the response of an independently selected subject receiving the test drug. The draft US FDA guidance suggests use of the difference ratio as a formulation for the bioequivalence criteria :

$$DR=\frac{Difference\ between\ test\ and\ reference\ drugs}{Difference\ between\ two\ reference\ drugs}\ .$$

For intersubject difference y_R-y_T and y_R-y_R', the moment-based measures becomes

$$d(y_T,y_R)=(\mu_T-\mu_R)^2+\sigma^2_{TT}+\sigma^2_{TR},,$$

$$d(y_R,y_R')=2\sigma^2_{TR}.$$

On the other hand, for intrasubject differences,

$$d(y_T,y_R)=(\mu_T-\mu_R)^2+\sigma^2_D+\sigma^2_{WT}+\sigma^2_{WR},,$$

$$d(y_R,y_R')=2\sigma^2_{WR}.$$

To address drug prescribability, the US FDA proposed the following aggregated, scaled moment-based one-sided criterion :

$$H_0:\xi\geq 0,\ H_1:\xi<0. \qquad (2)$$

where $\xi=(\mu_T-\mu_R)^2+\sigma^2_{TT}-\sigma^2_{TR}-\theta_P\max(\sigma^2_0,\sigma^2_{TR})$. Currently US FDA suggests $\theta_P=0.17448$ and $\sigma^2_0=0.04$. Since σ^2_{TR} is generally unknown, the calculation of $\max(\sigma^2_0,\sigma^2_{TR})$ depends on $\widehat{\sigma^2_{TR}}$. US FDA classifies reference-scaled criterion if $\sigma^2_{TR}>\sigma^2_0$, constant-scaled criterion, otherwise. The draft guidance suggests that a mixed-effects model in conjunction with the restricted maximum likelihood(RMIE) method be used to estimated total variances. If the upper 95% confidence bound is less than 0, then we conclude PBE.

Similarly IBS criterion proposed in the US FDA can be expressed as

$$H_0: \xi \geq 0,\ H_1: \xi < 0. \tag{3}$$

where $\xi = (\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 - \theta_I \max(\sigma_0^2, \sigma_{WR}^2)$ and σ_D^2 is the variance due to subject-by-formulation interaction. Currently US FDA suggests $\theta_I = 2.4948$ and we conclude IBE. $\sigma_0^2 = 0.04$ if the upper 95% confidence bound is less than 0.

4. Discussion

The proposed PBE and IBE criteria have resulted in valuable public discussion and debate. Although other criteria were considered in the extensive discussions, these criteria were chosen because of the clear links between the proposed moment-based criteria and the current ABE criteria. However, many concerns have been expressed (i) mean versus variance trade-off; (ii) resource implications; (iii) miscellaneous statistical issues; (iv) public health justification.

Especially questions have been raised with respect to the performance of the proposed aggregate criterion. There was a concern that since the PBE and IBE criteria include both the difference of means and difference of variances in one equation, bioequivalence might be concluded when neither the two means nor the two variances are close one another.

The restricted maximum likelihood(REML) analysis of mixed models, the proposed approach assumes normal distribution for error and random effects. A method of moments approach that does not make the normality assumption for point estimation is now preferred for this. Bootstrap method is also proposed.

Concerns were also expressed in power and sample size determination, replicated crossover design, missing data and outlier problems.

Chen(1997) outlined the desirable characteristics of BE criteria.

Table 1. Desirable features of bioequivalence criteria

1. Comparison of both average and variances
2. Assurance of switchability
3. Encouragement or reward of pharmaceutical companies to manufacture a better formulation
4. Control of type I error rate(consumer's risk) at 5%
5. Allowance for determination of sample size
6. Admission of the possibility of sequence and period effects as well as missing values
7. User-friendly software application for statistical methods
8. Provision of easy interpretation for scientist and clinicians
9. Minimization of increased cost for conducting BE studies

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