Bootstrap and MLS methods-based individual bioequivalence assessment

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Abstract—It is a one-sided hypothesis testing process for assessing bioequivalence. Bootstrap and modified large-sample (MLS) methods are considered to study individual bioequivalence (IBE), type I error and power of hypothesis tests are simulated and compared with FDA (2001). The results show that modified large-sample method is equivalent to the method of FDA (2001).

Keywords—individual bioequivalence; bootstrap; Bayesian bootstrap; modified large-sample

I. INTRODUCTION

The aim of bioequivalence (BE) studies is to assess the equivalence of two pharmaceutical drug products of the same active drug substance (Wijnand [1]). BE generally have three types including average bioequivalence (ABE), population bioequivalence (PBE) and individual bioequivalence (IBE). ABE focuses only on the difference of average measure between test drug (T) and reference drug (R), the interest measure may be area under curve and peak concentration. But ABE ignores the variability of the measure for T and R. PBE emphasizes total variability of the measure in population. IBE ignores the variability of the measure for T and R. PBE and IBE generally have three different sign. The 1-α upper confidence bound for 1/\eta = c_1\sigma_T^2 + \cdots + c_p\sigma_p^2 in which c_i (i = 1, 2, \ldots, p) has different sign. The 1-α upper confidence bound is

\[ c_1\sigma_T^2 + \cdots + c_p\sigma_p^2 + \sqrt{c_1^2\sigma_T^4\left(\frac{n_1}{u_1} - 1\right)^2 + \cdots + c_p^2\sigma_p^4\left(\frac{n_p}{u_p} - 1\right)^2}, \]

(1)

where

\[ u_i = \left\{ \begin{array}{ll} \frac{\sigma}{\hat{\sigma}_n} & c_i > 0, \\ \frac{\hat{\sigma}_n}{\sigma} & c_i < 0. \end{array} \right. \]

(2)

n_i denotes the number of samples in each sequence and \( \sigma_T^2, \sigma_R^2, \ldots, \sigma_p^2 \) are independent. Lee et al. [13] considered the case that \( \sigma_T^2, \sigma_R^2, \ldots, \sigma_p^2 \) are dependent and used the new method to evaluate PBE.

The rest of this article is organized as follows. In Section 2, we provide a description of the statistical model and criteria for evaluating IBE in Appendix G of FDA’s Guidance [3]. In Section 3, the power of different bootstrap methods and MLS method for test procedures is simulated, and the type I error of several tests is investigated. We present some conclusions in Section 4.

II. STATISTICAL MODEL AND CRITERIA

To assess IBE s-sequence and four-period experiment usually be considered. FDA [3] recommended the mixed-effect model

\[ Y_{ijkl} = \mu_k + \gamma_{ikl} + \delta_{ijk} + \epsilon_{ijkl} \]

(3)

where \( i = 1, 2, \ldots, s \) indicates sequence, \( j = 1, 2, \ldots, n_i \) indicates subject within sequence \( i \), \( k, R, T \) denote treatments, \( l = 1, 2 \) denotes replicate on treatment \( k \) for subjects within sequence \( i \). \( Y_{ijkl} \) is the response of replicate \( l \) on treatment \( k \) for subject \( j \) in sequence \( i \). \( \gamma_{ikl} \) represents the fixed effect of replicate \( l \) on treatment \( k \) in sequence \( i \), \( \delta_{ijk} \) is the random subject effect for subject \( j \) in sequence \( i \) on treatment \( k \), and \( \epsilon_{ijkl} \) is the random error for subject \( j \) within sequence \( i \) on replicate \( l \) of treatment \( k \).

The linearized criteria are as follows in FDA [3]

(a) reference-scaled \( (\sigma_{WR}^2 \geq \sigma_{W0}^2) \):

\[ \eta_1 = (\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_W^2 - \sigma_{WR}^2 \geq \theta_1 \cdot \sigma_{W0}^2. \]

(4)

(b) constant-scaled \( (\sigma_{WR}^2 < \sigma_{W0}^2) \):

\[ \eta_2 = (\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_W^2 - \sigma_{WR}^2 \geq \theta_1 \cdot \sigma_{W0}^2. \]

(5)

where \( \mu_T \) and \( \mu_R \) indicate population average responses of the log-transformed measure for the T and R formulation, respectively. \( \sigma_D^2 = \sigma_{BT}^2 + \sigma_{BR}^2 - 2\rho\sigma_{BT}\sigma_{BR} \) indicates subject-by-formulation interaction variance component, \( \sigma_W^2 \) and \( \sigma_{WR}^2 \)
represent the within-subject variance of the T formulation and R formulation, respectively. \( \sigma^2_{W0} \) represents specified constant within-subject variance and \( \theta_I \) BE limit. Consider the testing hypothesis

\[
H_0: \eta \geq 0 \quad \text{versus} \quad H_1: \eta < 0 \tag{6}
\]

where \( \eta = \eta_1 \) if \( \sigma^2_{WR} \geq \sigma^2_{W0} \) and \( \eta = \eta_2 \) if \( \sigma^2_{WR} < \sigma^2_{W0} \).

Some statistics are defined as follows:

- \( I_{ij} = Y_{ijT} - Y_{ijR} \), \( T_{ij} = Y_{ijT} - Y_{ijT2} \),
- \( R_{ij} = Y_{ijR1} - Y_{ijR2}, \) \( i=1,2,\ldots,s, j=1,2,\ldots,n_i \),
- \( Y_{ijT} = \frac{1}{2}(Y_{ijT1} + Y_{ijT2}), \) \( Y_{ijR} = \frac{1}{2}(Y_{ijR1} + Y_{ijR2}), \)

\[
\bar{\mu}_k = \frac{1}{s} \sum_{i=1}^{s} \sum_{j=1}^{n_i} Y_{ijkl}, \quad k=R,T.
\]

\[
\bar{\eta}_{io} = \frac{1}{s} \sum_{i=1}^{s} \sum_{j=1}^{n_i} Y_{ijkl} - \mu_T - \bar{\mu}_R. \tag{7}
\]

\[
M_I = \sigma^2_{WT} = \frac{1}{n_T} \sum_{i=1}^{s} \sum_{j=1}^{n_i} (T_{ij} - \overline{\eta}_{io})^2, \quad M_T = \sigma^2_{WR} = \frac{1}{n_r} \sum_{i=1}^{s} \sum_{j=1}^{n_i} (R_{ij} - \overline{\eta}_{io})^2, \quad M_R = \sigma^2_{WR} = \frac{1}{n_r} \sum_{i=1}^{s} \sum_{j=1}^{n_i} (R_{ij} - \overline{\eta}_{io})^2, \quad n_I = n_T = n_R = \sum_{i=1}^{s} n_i - s, \quad \overline{\eta}_{io} = \frac{1}{n_i} \sum_{j=1}^{n_i} R_{ij}, \quad \overline{\eta}_{io} = \frac{1}{n_i} \sum_{j=1}^{n_i} I_{ij}.
\]

Then the above linearized criteria are estimated by

(c) reference-scaled \( M_{RT} \geq \sigma^2_{W0} \):

\[
\tilde{\eta}_I = \hat{\Delta}^2 + M_I + 0.5M_T - (1.5 + \theta_I)M_R. \tag{8}
\]

(d) constant-scaled \( M_{RT} \leq \sigma^2_{W0} \):

\[
\tilde{\eta}_R = \hat{\Delta}^2 + M_I + 0.5M_T - 1.5M_R - \theta_I \sigma^2_{W0}. \tag{8}
\]

Compute the 95% upper bound of the parameter \( \eta \). If the upper bound is negative or zero, we can draw a conclusion that the IBE is equivalent for T and R. To calculate the upper bound there are parametric methods such as FDA [3] and nonparametric method(e.g., FDA [2]; Shao et al. [4]). On the basis of the mixed-model(FDA[3]), we study IBE using bootstrap and Bayesian bootstrap methods.

Note that

\[
\sigma^2_T = \text{var}(Y_{ijT1} + Y_{ijT2} - Y_{ijR1} - Y_{ijR2})/2, \quad \sigma^2_{WT} = \text{var}(Y_{ijT1} - Y_{ijT2})/2, \quad \sigma^2_{WR} = \text{var}(Y_{ijR1} - Y_{ijR2})/2, \quad \text{and} \quad \text{cov}(Y_{ijT1} - Y_{ijT2}, Y_{ijR1} - Y_{ijR2}) = 0, \quad \text{and} \quad \text{cov}(Y_{ijT1} + Y_{ijT2}, Y_{ijR1} + Y_{ijR2}) = 0, \quad \text{and} \quad \text{cov}(Y_{ijT1} + Y_{ijT2} - Y_{ijR1} - Y_{ijR2}, Y_{ijR1} - Y_{ijR2}) = 0.
\]

since \( \text{cov}(T_1, T_2) = \sigma^2_{WT}, \text{cov}(R_1, R_2) = \sigma^2_{WR}, \text{cov}(T_1, R_1) = \text{cov}(T_1, R_2) = \text{cov}(T_2, R_1) = \text{cov}(T_2, R_2) = \rho \sigma_{WT} \rho \sigma_{WR}. \) Hence \( M_I, M_T, M_R \) are independent.

III. Simulation Results

Given \( s=2 \) and \( n_1 = n_2 = n, \) let

\[
y_{ij} = (Y_{ijT1}, Y_{ijT2}, Y_{ijR1}, Y_{ijR2}), \quad y_{ij} = (Y_{ijT1}, Y_{ijT2}, Y_{ijR1}, Y_{ijR2}),
\]

\( (j = 1,2,\ldots,n) \), the bootstrap sample \( \{y_{i1}^*, y_{i2}^*, \ldots, y_{in}^*\} \) and \( \{y_{i1}^*, y_{i2}^*, \ldots, y_{in}^*\} \) are drawn from \( \{y_{i1}, y_{i2}, \ldots, y_{in}\} \) and \( \{y_{i1}, y_{i2}, \ldots, y_{in}\} \) with replacement, respectively.

We choose appropriate criterion to calculate \( \tilde{\eta}_I^* \) or \( \tilde{\eta}_R^* \), either \( \tilde{\eta}_I^* \) is noted by \( \tilde{\eta}_I^* \).

The following methods (M1-M4) can be found in [6].

(M1) bootstrap percentile method(BP): For each bootstrap sample, we calculate the bootstrap estimator \( M_{RT}^* \) of \( \sigma^2_{W0} \) to compare with \( \sigma^2_{W0} = 0.04 \) so as to choose the approximate criterion. Repeat the above step B times (choose B=500), we can calculate the bootstrap estimator \( \tilde{\eta}^*_B(b = 1,2,\ldots,B) \) of \( \eta \), let \( \tilde{\eta}^*_B(i) \) represent the \( i-th \) largest number of \( \tilde{\eta}^*_B(b = 1,2,\ldots,B) \). The approximate 100(1 – \( \alpha \)) confidence upper bound is \( \tilde{\eta}^*_B(B - Boa) \) for \( \eta \). IBE is equivalent to T and R if \( \tilde{\eta}^*_B(B - Boa) \leq 0 \).

(M2) hybrid bootstrap percentile method(HBP): We analogously compute the approximate 100(1– \( \alpha \)) confidence upper bound for \( \eta \) is \( 2\tilde{\eta} - \tilde{\eta}^*_B(Boa) \). IBE is equivalent to T and R if \( 2\tilde{\eta} - \tilde{\eta}^*_B(Boa) \leq 0 \).

(M3) Bayesian bootstrap percentile method(BBP): To estimate the interest parameters \( \Delta, \sigma^2_I, \sigma^2_{WT} \) and \( \sigma^2_{WR} \), we generate \( s \) random vectors \( V_i = D(n_i; 1,1,1,\ldots,1) \) \( i=1,2,\ldots,s \). Then the Bayesian bootstrap estimator of \( \Delta \) is

\[
\Delta^* = \frac{1}{s} \sum_{i=1}^{s} \sum_{j=1}^{n_i} V_{ij}. \tag{9}
\]

The Bayesian bootstrap estimators of \( \sigma^2_I, \sigma^2_{WT} \) and \( \sigma^2_{WR} \) are

\[
M_I^* = \frac{1}{n_T} \sum_{i=1}^{s} \sum_{j=1}^{n_i} V_{ij}(I_{ij} - \frac{n_i}{n_T} V_{ij}), \tag{10}
\]

\[
M_T^* = \frac{1}{2n_T} \sum_{i=1}^{s} \sum_{j=1}^{n_i} V_{ij}(T_{ij} - \frac{n_i}{n_T} V_{ij}), \tag{11}
\]

and

\[
M_R^* = \frac{1}{2n_T} \sum_{i=1}^{s} \sum_{j=1}^{n_i} V_{ij}(R_{ij} - \frac{n_i}{n_T} V_{ij}), \tag{12}
\]

respectively. Denoted Bayesian bootstrap estimator of \( \eta \) by \( \tilde{\eta}^*_B \). IBE is equivalent to T and R if \( \tilde{\eta}^*_B(B - Boa) \leq 0 \).

(M4) hybrid Bayesian bootstrap percentile method(HBBP): The process for assessing IBE is similar to Bayesian bootstrap percentile method. IBE can be claimed for T and R if \( 2\tilde{\eta} - \tilde{\eta}^*_B(Boa) \leq 0 \).

(M5) by the work of Section 2 we use formulas (1) and (2) to calculate the upper confidence bound for the parameter \( \eta \).
The following parameter setting to enable \( H_0 \) hold is considered (\( ps \) represents parameter setting).

<table>
<thead>
<tr>
<th>( ps )</th>
<th>( \mu_T - \mu_R )</th>
<th>( \sigma^2_{u_T} )</th>
<th>( \sigma^4_{u_T} )</th>
<th>( \sigma^2_{u_R} )</th>
<th>( \sigma^4_{u_R} )</th>
<th>( \rho )</th>
<th>( \eta )</th>
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<tr>
<td>1</td>
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<td>0.06</td>
<td>0.01</td>
<td>0.03</td>
<td>0.01</td>
<td>0.09</td>
<td>0.0490</td>
</tr>
<tr>
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<td>0.04</td>
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</tr>
<tr>
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<td>0.01</td>
<td>0.03</td>
<td>0.02</td>
<td>0.09</td>
<td>0.0262</td>
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</table>

The above six methods are used to evaluate IBE for the dataset in [1]. Let \( \alpha = 0.05 \), the 1 – \( \alpha \) upper confidence bound are -0.0305, -0.0425, -0.0506, -0.0505, -0.0471 and -0.0316, respectively, the smallest number is -0.0505 which is associated with Bayesian bootstrap percentile method.

TABLE I

<table>
<thead>
<tr>
<th>METHOD</th>
<th>( \beta ) (n=12)</th>
<th>( \beta ) (n=24)</th>
<th>( \beta ) (n=36)</th>
<th>( \beta ) (n=48)</th>
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<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
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<td>0.72</td>
<td>0.73</td>
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<tr>
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<td>0.83</td>
<td>0.90</td>
<td>0.98</td>
</tr>
<tr>
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<td>1</td>
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</tr>
<tr>
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<td>0.81</td>
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<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>HBBP</td>
<td>0.81</td>
<td>0.90</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
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<tr>
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<tr>
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<td>1</td>
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<tr>
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</tr>
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<td>0.79</td>
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</tr>
<tr>
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REFERENCES


