ABSTRACT

As stated by the United States Food and Drug Administration (FDA), an approved generic drug, which is regulated according to average bioequivalence, can be used as a substitute for the innovative drug. However, FDA does not indicate that two generic copies of the same innovative drug can be used interchangeably, even though they are bioequivalent to the same brand-name drug. Along with such an undetermined fact, it attracts increasing concerns about whether the approved generic drug has the same therapeutic effect as the brand-name drug. That is concerning about whether they can be used interchangeably.

Four criteria are reviewed in this poster for assessment of bioequivalence of generic drug products. The criteria include: average bioequivalence criterion (ABE), a $\sigma_D^2$ criterion (the variance due to subject-by-drug interaction), and a scaled average bioequivalence (SCDI) criterion. In addition, by extending the idea of reverse of test and reference product, a new criterion for the assessment of interchangeability is proposed.

Keywords
Biosimilars; Generic drugs; Average bioequivalence (ABE); Within and Between Subject variance; Scaled average bioequivalence (SABE); Scaled criterion for drug interchangeability (SCDI).

INTRODUCTION

As indicated by the FDA, an approved generic drug of an innovative drug can serve as a substitute for the reference product. FDA, however, did not indicate that the approved generic drug and the innovative drug can be used interchangeably.

But as more generic drug products become available, it is a concern whether the approved generic drug products have the same quality and therapeutic effect as the brand-name drug product and whether they can be used safely and interchangeably.

The issue of drug interchangeability has been discussed tremendously among the regulatory agency, pharmaceutical industry. In the next sections, four criteria for assessment of drug interchangeability are discussed.

Criteria 1. Criteria for Average Bioequivalence (ABE)

For IBE, the criteria has the following form:

$$\theta = \frac{\delta + \sigma_D^2}{\sigma_D^2} \epsilon, \quad \epsilon \sim N(0, 1)$$

where $\delta = \mu_T - \mu_R$, what’s more, $\sigma_D^2$ is the variance component due to subject-by-treatment interaction between drug products, $\sigma_D^2$ and $\sigma_D^2$ are intra-subject variances for the reference product and the test product, respectively.

The ABE criteria has the form which is quite alike the above. But the denominator is simply $\sigma_D^2$. And bioequivalence is then claimed if the 90% CI for the geometric mean ratio (GMR) between the T and R falls entirely within the (80.0%, 125.0%).

Criteria 2. Criteria based on $\sigma_D^2$

$$\sigma_D^2 = \sigma_T^2 + \sigma_R^2 - 2\rho \sigma_T \sigma_R$$

where $\mu$ is the overall mean, $F_i$ is the fixed effect of the ith drug product (replicated 2x2 crossover design: RTTR, TRTR), $W_i$’s are other fixed effects, and $S_{ij}$ is the random effect of the jth subject in the kth sequence under the ith drug product.

Thus, we test whether $\sigma_D^2 < 0.15$ for drug interchangeability.

Criteria 3. Scaled Criterion for Drug Interchangeability (SCDI)

Step 1: Unscaled ABE criterion

Let $BEL$ be the limit of $S/4$. Thus, as mentioned in criteria 1:

$$\frac{1}{BEL} \leq \text{GMR} \leq BEL$$

which implies that

$$-\log(BEL) \leq \mu_T - \mu_R \leq \log(BEL)$$

Where $\mu_T$ and $\mu_R$ are logarithmic means.

Step 2: Scaled ABE (SABE) criterion

Difference in logarithmic means is adjusted for intra-subject variability as follows:

$$-\log(BEL) \leq \frac{\mu_T - \mu_R}{\sigma^2} \leq \log(BEL)$$

Therefore, SCDI is given by

$$-\log(BELS) \leq \frac{\mu_T - \mu_R}{\sigma^2} \leq \log(BELS)$$

where $\sigma_{iw}$ is a within-subject variation and BELS is the BE limit for SABE.

In practice, $\sigma_{iw}$, the within-subject variation of the reference product is often considered.

Step 3: Proposed scaled criterion for drug interchangeability (SCDI)

Consider the first two components of the IBE, we have the following relationship:

$$-\log(BELS) \leq \frac{\mu_T - \mu_R}{\sigma^2} \leq \log(BELS)$$

Thus, SCDI is given by

$$-\log(BELS) \leq \frac{\mu_T - \mu_R}{\sigma^2} \leq \log(BELS)$$

Criteria 4. Alternative Criterion based on Reverse of Test and Reference

As mentioned, if the 90% CI for the GMR (i.e., $\mu_T/\mu_R$), say ($L_1$, $U_1$), is totally within (0.8, 1.25), then we can switch from T to R.

Then by similar idea, if the 90% CI for the GMR (i.e., $\mu_R/\mu_T$), say ($L_2$, $U_2$), is totally within (0.8, 1.25), then we can switch from R to T.

Thus we can conclude that T and R are interchangeable.

As a test statistic, let $p_T = P_{1}(\text{switch from T to R and 2}): P_{2}(\text{switch from R to T}) > \max (p_T, p_R)$. Thus, point estimates and the corresponding CIs for $p_T$, $p_R = 1, 2, 3$, are necessarily obtained for this criteria regards to $P_T$.

DISCUSSION

It is a concern whether the approved generic drug products can be used interchangeably in terms of their quality, safety, and efficacy as compared to the innovative drug product. It is also recognized that bioequivalence assessment based on average bioavailability by ignoring the heterogeneity in variabilities between the test and the reference product does not guarantee drug interchangeability.

Although some criteria for drug interchangeability have been proposed in the past decade, none of these criteria work satisfactory for addressing drug prescribability and switchability. On the other hand, the SCDI criterion stated above which adjusted for the intra-subject variability and the variability due to subject-by-treatment interaction seems reasonable. Also, the newly proposed criterion by reversing the test and the reference product may provide a simple answer to a complicated problem. The proposed criteria for drug interchangeability for generic approval of small molecule drug products can be directly applied to the assessment of interchangeability for biosimilar products. However, further evaluation of their statistical properties and/or performances are necessarily conducted.

REFERENCE