2015 Duke-Industry Statistics Symposium

On Criteria for Assessing Drug Interchangeability in Bioequivalence /Biosimilarity

Meng Chen [1], Shein-Chung Chow [2]

1. Meng Chen, Research Assistant, Duke Department of Biostatistics and Bioinformatics
2. Shein-Chung Chow, Professor, Duke Department of Biostatistics and Bioinformatics

Duke Department of Biostatistics & Bioinformatics
Duke University School of Medicine

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 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 criterion are reviewed in this poster for assessment of bioequivalence of generic drug products. The criterion include: average bioequivalence criterion (ABE), a $\sigma_D{}^2$ (the variance due to subject-by-drug interaction) related criterion, 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).

FUNDING

This research is partially supported by the Duke University Center for AIDS Research, an NIH-funded program.

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 interchangeability.
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 criterion for assessment of drug interchangeability are discussed.

Criteria 1. Criteria for Average Bioequivalence (ABE)

For IBE, the criteria has the following form: $\theta_I = (\delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2)/\max\{\sigma_{W0}^2, \sigma_{WR}^2\}$, where $\delta = \mu_T - \mu_R$. What's more, σ_{D^2} is the variance component due to subject-by-treatment interaction between drug products, σ_{WR^2} and σ_{WT^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 σ_{WR^2}. And bioequivalence is then claimed if the 90% CI for the geometric means ratio (GMR) between the T and R falls entirely within the (80.00%, 125.00%).

Criteria 2. Criteria based on σ_D

$$y_{ijk} = \mu + F_l + W_{ljk} + S_{ikl} + \epsilon_{ijk}$$

where μ is the overall mean, F_l is the fixed effect of the lth drug product (replicated 2x2 crossover design: RTRT, TRTR), W_{ljk}'s are other fixed effects, and S_{ijk} is the random effect of the i^{th} subject in the kth sequence under the lth drug product.

$$\sigma_D^2 = \sigma_{BT}^2 + \sigma_{BR}^2 - 2\rho\sigma_{BT}\sigma_{BR}$$

which is variance of $S_{ikT} - S_{ikR}$. σ_D^2 is usually referred to as the variance due to the subject-by-drug interaction.

Thus, we Test whether $\sigma_D > 0.15$ for drug interchangeability.

Criteria 3. Scaled Criterion for Drug Interchangeability (SCDI)

Step 1: Unscaled ABE criterion

Let BEL be limit of 5/4. Thus, as mentioned in criteria 1:

$\frac{1}{BEL} \le GMR \le BEL$, which implies that $-log(BEL) \le \mu_T - \mu_R \le log(BEL)$

Where μ_T and μ_R are logarithmic means.

Step 2: Scaled ABE (SABE) criterion

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

$$-log(BELS) \le \frac{\mu_T - \mu_R}{\sigma_W} \le log(BELS),$$

Where σ_{W^2} is a within-subject variation and *BELS* is the BE limit for SABE.

In practice, σ_{WR^2}, 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:

$\frac{\delta^2 + \sigma_D^2}{\sigma_W^2} \approx \frac{2\delta\sigma_D}{\sigma_W^2}$

Thus, SCDI is given by $-log(BELS)f\sigma_W \le \mu_T - \mu_R \le log(BELS)f\sigma_W$, where $f = \sigma_W/(2\sigma_D)$.

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

As mentioned, if the 90% CI for the GMR (i.e., μ_T/μ_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., μ_R/μ_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.

$p_3 = P(1: \text{Switch from T to R } and\ 2: \text{switch from R to T}) > \max(p_1, p_2)$. Thus, point estimates and the corresponding CIs for p_i, $i = 1,2,3$, are necessarily obtained for this criteria regards to p_3.

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

Chow S C, Liu J P. Design and analysis of clinical trials: concepts and methodologies[M]. John Wiley & Sons, 2008.