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Drug Interchangeability in Bioequivalence and Biosimilar Studies

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Received Date: 20st November 2021
Accepted Date: 15th December 2021
Published Date: 26th December 2021

Citation: Chow S-C, Li Y. Drug Interchangeability in Bioequivalence and Biosimilar Studies. Enliven: Biosimilars Bioavailab. 2021; 5(1): 002.

1) Abstract

In the United States, when an innovative (brand-name) drug or biological product is going off patent, pharmaceutical and/or generic/biotech companies may file an abbreviated new drug application (ANDA) for approval of generic drugs FDA [1] or a Biologic License Application (BLA) for approval of biosimilar products of the brand-name drug product [2]. As more and more generic drugs (biosimilar products) become available in the marketplace, it is a public concern that (i) whether the quality, safety, and/or efficacy of these generic drugs (biosimilar products) work as well as that of the brand-name drug product and (ii) whether these generic drugs (biosimilar products) can be used interchangeably among generic drugs (biosimilar products) and the brand-name drug product. This article provides a comprehensive review of the concept, criteria, design, and analysis method for assessment of drug interchangeability of generic drugs and biosimilar products. In addition, some challenging issues that are commonly encountered when assessing drug interchangeability are discussed.

2) Keywords: Drug prescribability; Drug switchability; Switching and alternation; Replicated crossover design; N-of-1 design

1. Introduction

In the United States (US), when an innovative (brand-name) drug product is going off patent, pharmaceutical and/or generic/biotech companies may file an abbreviated new drug application (ANDA) for approval of generic copies or a Biologic License Application (BLA) for approval of biosimilar products of the brand-name drug product. The US Food and Drug Administration (FDA) indicates that an approved generic drug or an approved biosimilar product can serve as a substitute for its brand-name drug. However, FDA does not indicate that an approved generic drug or an approved biosimilar product and the brand-name drug can be used interchangeably. As more generic drugs and biosimilar products become available in the marketplace, it is a public concern whether the generic drugs and biosimilar products work as well as the brand-name drug products in terms of their quality, safety, and efficacy. In addition, it is a great safety concern especially when a patient is to switch from one generic drug (or biosimilar product) to another.

The concepts and regulatory requirements regarding drug interchangeability of generic drugs and biosimilar products are similar but different. For example, for the development of generic drugs, drug interchangeability is usually classified as either drug prescribability or drug switchability. Drug prescribability is referred to as the physician's choice for prescribing an appropriate drug for new patients among the drug products available, while drug switchability is related to the switch from a drug product to an alternative drug within the same patient whose concentration of the drug product has been titrated to a steady, efficacious and safe level [3,4]. For biosimilar products, on the other hand, under the US Biologics Price Competition and Innovation (BPCI) Act of 2009, a biological product is considered to be interchangeable with the reference product if (i) the biological product is biosimilar to the reference product; and (ii) it can be expected to produce the same clinical result in any given patient. In addition, for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. Thus, drug interchangeability for biosimilar products focuses on relative risk with/without switching and alternation [5-7].

Since the concepts of drug interchangeability for generic drugs and for biosimilar products are different, criteria, design, and analysis methods for assessment of drug interchangeability for generic drugs and biosimilar products are also different. The purpose of this article is to provide a comprehensive review of drug interchangeability for both generic drugs and biosimilar products. In the subsequent sections, concepts, criteria, design, and statistical methods for assessment of drug interchangeability of generic drugs and biosimilar products are reviewed in Section 2 and Section 3, respectively. Some challenging issues when assessing drug interchangeability are discussed in Section 4. Section 5 provides some concluding remarks.

2. Drug Interchangeability for Generic Drugs

Under the Fundamental Bioequivalence Assumption [4], when a generic drug is claimed bioequivalent to a brand-name drug, it is assumed that they are therapeutically equivalent. FDA indicates that an approved generic drug can be used as a substitute for the brand-name drug. However, FDA does not indicate that two generic copies of the same brand-name drug can be used interchangeably even though they are bioequivalent to the same brand-name drug. In practice, bioequivalence between generic copies of the same brand-name drug is not required. However, 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.

2.1 Drug Prescribability and Drug Switchability

The concepts of drug interchangeability for generic drugs can be classified as either drug prescribability or drug switchability. Drug prescribability is referred to as the physician's choice for prescribing an appropriate drug for new patients among the drug products available, while drug switchability is related to the switch from a drug product to an alternative drug for the same patient whose concentration of the drug product has been titrated to a steady, efficacious and safe level [3,4].

2.2 Population Bioequivalence and Individual Bioequivalence

To evaluate whether the generic drug products can be used safely and interchangeably, the FDA suggests population bioequivalence and individual bioequivalence be assessed for addressing drug prescribability and drug switchability of approved generic drug products, respectively [1,8]. The concepts and statistical methods for assessment of drug prescribability and drug switchability are briefly described below.

Population bioequivalence (PBE)

To address drug prescribability, the FDA recommends that population bioequivalence (PBE) be assessed. In addition to the average of bioavailability, PBE focuses on the variability of bioavailability. The 2001 FDA guidance recommends the following criterion be used for assessing PBE:

$$\theta_P = (\delta^2 + \sigma_{TT}^2 - \sigma_{TR}^2)/\max\{\sigma_{T0}^2, \sigma_{TR}^2\}, \sqrt{2}$$

where $\sigma_{TT}^2, \sigma_{TR}^2$ are the total variances for the test product and the reference product, respectively and σ_{T0}^2 is the scale parameter specified by the regulatory agency or the sponsor. PBE can be claimed if the one-sided 95% upper confidence bound for θ_P is less than a pre-specified bioequivalence limit. In view of the above PBE criterion, PBE can be claimed if the null hypothesis in

$$H_0: \lambda \geq 0 \quad \text{vs.} \quad H_a: \lambda < 0$$

is rejected at the 5% level of significance and the observed geometric means ratio (GMR) is within the limits of 80% and 125%, where

$$\lambda = \delta^2 + \sigma_{TT}^2 - \sigma_{TR}^2 - \theta_{PBE} \max(\sigma_{TR}^2, \sigma_0^2)$$

and θ_{PBE} is a constant specified in the 2001 FDA draft guidance. Under a 2x2 crossover design, the one-sided 95% upper confidence bound for θ_P can be obtained under the following model:

$$y_{ijk} = \mu + F_l + P_j + Q_k + S_{ikl} + \epsilon_{ijk} \qquad (1)$$

where μ is the overall mean, P_j is the fixed effect of the j*th* period, Q_k is the fixed effect of the *k*th sequence, F_l is the fixed effect of the *l*th drug product, S_{ijk} is the random effect of the *l*th subject in the *k*th sequence under the *l*th drug product, and ϵ_{ijk}'s are independent random errors distributed as $N(0,\sigma_{Wl}^2)$. It is assumed that S_{ijk}'s and ϵ_{ijk}'s are mutually independent. It can be verified that (S_{ikT}, S_{ikR}), $i=1,2,\ldots,n_k$; $k=1,2$ are independent and identically distributed bivariate normal random vectors with mean 0 and an unknown covariance matrix

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

where σ_{Bl}^2 denotes the between-subject variability for the lth drug product. Thus, we have

$$\sigma_{TT}^2 = \sigma_{BT}^2 + \sigma_{WT}^2 \text{ and } \sigma_{TR}^2 = \sigma_{BR}^2 + \sigma_{WR}^2.$$

Under model (1), unbiased estimators for δ, σ_{TT}^2, and σ_{TR}^2 can be obtained as follows

$$\hat{\delta} = \frac{\bar{y}_{11} - \bar{y}_{12} - \bar{y}_{21} + \bar{y}_{22}}{2} \sim N\left(\delta, \frac{\sigma_{l,1}^2}{4}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)\right),$$

where $\bar{y}_{jk}$ is the sample mean of the observations in the k_{th} sequence at the j_{th} period and $\sigma_{l,1}^2$ is $\sigma_{a,b}^2 = \sigma_D^2 + a\sigma_{WT}^2 + b\sigma_{WR}^2$ with $a=1$ and $b=1$. Commonly considered unbiased estimators for σ_{TT}^2 and σ_{TR}^2 are given by

$$\hat{\sigma}_{TT}^2 = \frac{1}{n_1 + n_2 - 2}\left[\sum_{i=1}^{n_1}(y_{i11} - \bar{y}_{11})^2 + \sum_{i=1}^{n_2}(y_{i22} - \bar{y}_{22})^2\right] \sim \frac{\sigma_{TT}^2 \lambda_{n_1+n_2-2}^2}{n_1+n_2-2}$$

and

$$\hat{\sigma}_{TR}^2 = \frac{1}{n_1+n_2-2}\left[\sum_{i=1}^{n_1}(y_{i21} - \bar{y}_{21})^2 + \sum_{i=1}^{n_2}(y_{i12} - \bar{y}_{12})^2\right] \sim \frac{\sigma_{TR}^2 \lambda_{n_1+n_2-2}^2}{n_1+n_2-2}$$

By Chow, Shao, and Wang [9], the following approximate 95% upper confidence bound for λ when $\sigma_{TR}^2 \geq \sigma_0^2$ can be obtained:

$$\hat{\lambda}_U = \hat{\delta}^2 + \hat{\sigma}_{TT}^2 - (1 + \theta_{PBE})\hat{\sigma}_{TR}^2 + t_{0.05, n_1+n_2-2}\sqrt{V},$$

where V is an estimated variance of $\hat{\delta}^2 + \hat{\sigma}_{TT}^2 - (1 + \theta_{PBE})\hat{\sigma}_{TR}^2$ of the form

$$V = \left(2\hat{\delta}, 1, -(1 + \theta_{PBE})\right) C \left(2\hat{\delta}, 1, -(1 + \theta_{PBE})\right)'$$

and C is an estimated variance-covariance matrix of $(\hat{\delta}, \hat{\sigma}_{TT}^2, \hat{\sigma}_{TR}^2)$. Since $\hat{\delta}$ and $(\hat{\sigma}_{TT}^2, \hat{\sigma}_{TR}^2)$ are independent, C is given by

$$C = \begin{pmatrix} \frac{\sigma_{i,1}^2}{4}\left(\frac{1}{n_1}+\frac{1}{n_2}\right) & (0,0) \\ (0,0)' & \frac{(n_1-1)C_1}{(n_1+n_2-2)^2}+\frac{(n_2-1)C_2}{(n_1+n_2-2)^2} \end{pmatrix},$$

where C_1 is sample covariance matrix of $((y_{i11}-\bar{y}_{11})^2, (y_{i21}-\bar{y}_{21})^2)$, i=1,2,…,n_1, and C_2 is sample covariance matrix of $((y_{i22}-\bar{y}_{22})^2, (y_{i12}-\bar{y}_{12})^2)$, i=1,2,…,n_2. On the other hand, when $\sigma_{TR}^2 < \sigma_0^2$, the upper confidence bound for λ should be modified as follows:

$$\hat{\lambda}_U = \hat{\delta}^2 + \hat{\sigma}_{TT}^2 - (1+\theta_{PBE})\hat{\sigma}_0^2 + t_{0.05,n_1+n_2-2}\sqrt{V_0},$$

where $V_0 = (2\hat{\delta}, 1, -1)C(2\hat{\delta}, 1, -1)'$.

Individual Bioequivalence (IBE):

To address drug switchability, the FDA suggests that individual bioequivalence (IBE) be assessed under replicated crossover designs such as a replicated 2x2 crossover design, i.e., (TRTR, RTRT) or a 2x3 two-sequence dual design, i.e., (TRT, RTR). In addition to the average of bioavailability, IBE focuses on the variability of bioavailability and variability due to subject-by-drug interaction. The 2001 FDA guidance recommends the following criterion be used for assessing IBE:

$$\theta_I = (\delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2)/\max\{\sigma_{W0}^2, \sigma_{WR}^2\},$$

where $\delta = \mu_T - \mu_R$, $\sigma_{WT}^2, \sigma_{WR}^2, \sigma_D^2$ are the true difference in means, intra-subject variabilities of the test product and the reference product, and variance due to subject-by-formulation interaction between drug products, respectively. σ_{W0}^2 is the scale parameter specified by the regulatory agency or the sponsor. In view of the above IBE criterion, IBE can be claimed if the null hypothesis in

$$H_0: \gamma \geq 0 \quad vs. \quad H_a: \gamma < 0$$

is rejected at the 5% level of significance and the observed geometric means ratio (GMR) is within the limits of 80% and 125%, where

$$\gamma = \delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2 - \theta_{IBE}\max(\sigma_{WR}^2, \sigma_{W0}^2)$$

and θ_{IBE} is a constant specified in the 2001 FDA draft guidance.

To the assessment of IBE, FDA recommends a replicated 2x2 crossover design, i.e., (TRTR, RTRT) or (RTRT, TRTR) be used. Under the 2x2 replicated crossover design, the one-sided 95% upper confidence bound for θ_I can be obtained under the following statistical model:

$$y_{ijk} = \mu + F_l + W_{ljk} + S_{ikl} + \epsilon_{ijk}, \qquad (2)$$

where μ is the overall mean, F_l is the fixed effect of the lth drug product, W_{ljk}'s are fixed period, sequence, and interaction effects, and S_{ijk} is the random effect of the ith subject in the kth sequence under the lth drug product, and ϵ_{ijk}'s are independent random errors distributed as $N(0, \sigma_{Wl}^2)$. It is assumed that S_{ijk}'s and ϵ_{ijk}'s are mutually independent. Under model (2), σ_D^2 is given by

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

which is the variance of $S_{ikT} - S_{ikR}$. Note that σ_D^2 is usually referred to as the variance due to the subject-by-drug interaction. It can be verified that when $\sigma_{WR}^2 \geq \sigma_{W0}^2$, the linearized criterion γ can be decomposed as follows:

$$\gamma = \delta^2 + \sigma_{0.5,0.5}^2 + 0.5\sigma_{WT}^2 - (1.5+\theta_{IBE})\sigma_{WR}^2.$$

Now, under model (2), for subject i in sequence k, let x_{ilk} and z_{ilk} be the average and the difference, respectively, of the observations from drug product l and let $\bar{x}_{lk}$ and $\bar{z}_{lk}$ be respectively the sample mean based on x_{ilk}'s and z_{ilk}'s. Thus, under model (2), unbiased estimators for δ, $\sigma_{0.5,0.5}^2$, and σ_{WR}^2 can be obtained as follows

$$\hat{\delta} = \frac{\bar{x}_{T1}-\bar{x}_{R1}+\bar{x}_{T2}-\bar{x}_{R2}}{2} \sim N\left(\delta, \frac{\sigma_{0.5,0.5}^2}{4}\left(\frac{1}{n_1}+\frac{1}{n_2}\right)\right),$$

$$\hat{\sigma}_{0.5,0.5}^2 = \frac{(n_1-1)s_{d1}^2+(n_2-1)s_{d2}^2}{n_1+n_2-2} \sim \frac{\sigma_{0.5,0.5}^2\lambda_{n_1+n_2-2}^2}{n_1+n_2-2},$$

where s_{dk}^2 is the sample variance based on $x_{iTk} - x_{iRk}$, i=1,2,…, n_k; an unbiased estimator of σ_{WT}^2 is given by

$$\hat{\sigma}_{WT}^2 = \frac{(n_1-1)s_{T1}^2 + (n_2-1)s_{T2}^2}{n_1+n_2-2} \sim \frac{\sigma_{WT}^2\lambda_{n_1+n_2-2}^2}{n_1+n_2-2},$$

where s_{Tk}^2 is the sample variance based on z_{iTk},i = 1,2,…,n_k; an unbiased estimator of σ_{WR}^2 is given by

$$\hat{\sigma}_{WR}^2 = \frac{(n_1-1)s_{R1}^2+(n_2-1)s_{R2}^2}{n_1+n_2-2} \sim \frac{\sigma_{WR}^2\lambda_{n_1+n_2-2}^2}{n_1+n_2-2},$$

where S_{dk}^2 is the sample variance based on z_{iRk},i=1,2,…, n_k. Furthermore, since $\hat{\delta}, \hat{\sigma}_{0.5,0.5}^2, \hat{\sigma}_{WT}^2, and\ \hat{\sigma}_{WR}^2$ are independent, when $\sigma_{WR}^2 \geq \sigma_{W0}^2$ an approximate 95% confidence upper bound for γ can be obtained as follows

$$\hat{\gamma}_U = \hat{\delta}^2 + \hat{\sigma}_{0.5,0.5}^2 + 0.5\hat{\sigma}_{WT}^2 - (1.5+\theta_{IBE})\hat{\sigma}_{WR}^2 + \sqrt{U},$$

where U is the sum of the following four quantities:

$$\left[\left(|\hat{\delta}| + t_{0.05,n_1+n_2-2}\frac{\hat{\sigma}_{0.5,0.5}}{2}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}\right)^2 - \hat{\delta}^2\right]^2,$$

$$\hat{\sigma}_{0.5,0.5}^4\left(\frac{n_1+n_2-2}{\lambda_{0.05,n_1+n_2-2,}^2}-1\right)^2,$$

$$0.5^2\hat{\sigma}_{WT}^4\left(\frac{n_1+n_2-2}{\lambda_{0.05,n_1+n_2-2,}^2}-1\right)^2,$$

and

$$(1.5+\theta_{IBE})^2\hat{\sigma}_{WR}^4\left(\frac{n_1+n_2-2}{\lambda_{0.05,n_1+n_2-2,}^2}-1\right)^2.$$

When $\sigma_{WR}^2 < \sigma_{W0}^2$, an approximate 95% confidence upper bound for γ is given by

$$\hat{\gamma}_U = \hat{\delta}^2 + \hat{\sigma}_{0.5,0.5}^2 + 0.5\hat{\sigma}_{WT}^2 - 1.5\hat{\sigma}_{WR}^2 - \theta_{IPE}\sigma_{W0}^2 + \sqrt{U_0},$$

where U_0 is the sum as U except that the four quantities should be replaced by

$$1.5^2\hat{\sigma}_{WR}^4\left(\frac{n_1+n_2-2}{\lambda_{0.05,n_1+n_2-2,}^2}-1\right)^2.$$

3 Drug Interchangeability for Biosimilar Products

As indicated in the Subsection (b) (3) of BPCI Act amended to the Public Health Act Subsection 351(k)(3) [17], the term *interchangeable or interchangeability* in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. Along this line, in what follows, definition and basic concepts of interchangeability (in terms of switching and alternating) are given.

3.1 Definition and Basic Concepts

As indicated in the Subsection (a)(2) amends the Public Health Act Subsection 351(k)(3), an interchangeable biosimilar product is defined as a biosimilar product that is biosimilar to the reference product and it can be expected to produce the same clinical result in *any given patient*. In addition, the biosimilar product that is administered more than once to an individual in terms of safety or diminished efficacy of switching and alternation between use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

It should be noted that when FDA declares the biosimilarity of two drug products, it may not be assumed that they are interchangeable. Therefore, labels ought to state whether, for a follow-on biologic that is biosimilar to a reference product, interchangeability has or has not been established. However, payers and physicians may, in some cases, switch products even if interchangeability has not been established.

3.2 Switching and Alternation

Unlike drug interchangeability (in terms of prescribability and switchability), the FDA has a slightly perception of drug interchangeability for biosimilars. From the FDA's perspective, interchangeability includes the concept of switching and alternation between an innovative biologic product (R) and its biosimilar (T) products. The concept of switching is referred to as not only the switch from "R to T" or "T to R" (narrow sense of switchability), but also "T to T" and "R to R" (broader sense of switchability). In its guidance, FDA defines *switching* as a single switch from a biosimilar or brand-name product to a biosimilar or brand-name drug (FDA, 2017). Thus, in order to assess the risk of with/without *switching*, biosimilarity for "R to T", "T to R", "T to T", and "R to R" need to be assessed based on some biosimilarity criteria under a valid study design.

On the other hand, the concept of alternation is referred to as *multiple* switches (FDA, 2017). For example, the switch from T to R and then switch back to T (i.e., "T to R to T") or the switch from R to T and then switch back to R (i.e., "R to T to R"). Thus, the difference between "the switch from T to R" then "the switch from R to T" and "the switch from R to T" then "the switch from T to R" needs to be assessed for addressing the risk of with/without alternation.

3.3 Study Design

Since FDA interprets the risk of switch and alternation as the result of a single switch and multiple switches, respectively, we focus on the design and analysis of switching designs in biosimilar drug development. In its recent draft guidance, the FDA recommended a $2 \times (m + 1)$ crossover design as the switching design to assess the risk between switching/alternation and without switching/alternation, where m is the number of switches [7]. In other words, FDA recommends a 2 × 2 crossover design of (RT, RR) be used for evaluation of the risk between with/without switching (i.e., single switch). For evaluation of the risk between with/without alternation, FDA suggests a 2 × 3 crossover design of (RTR, RRR) with two switches should be used, while a 2 × 4 crossover design of (RTRT, RRRR) with three switches should be considered.

Alternatively, Chow and Lee [10] introduced the use of a complete n-of-1 trial design. Chow and Lee [10] indicated that the FDA-recommended $2 \times (m + 1)$ switching designs are special cases of complete n-of-1 trial designs with *m* switches.

In their article, Chow and Lee [10] also studied the sample size requirements and statistical methods for data analysis under these switching designs. The results showed that FDA's recommended switching designs are not efficient as compared to the complete n-of-1 trial design.

3.4 Statistical Methods

Under the FDA's recommended switching designs or the complete n-of-1 trial design, standard statistical methods for evaluation of the relative risk between with and without switching and alternation under a standard crossover design such as (RT, TR) are not appropriate. Alternatively, Chow [11] proposed the idea of using biosimilarity index which was derived based on the probability of reproducibility following the idea proposed by Shao and Chow [12]. Shao and Chow [12] proposed a reproducibility probability as an index for determining whether it is necessary to require a second trial when the result of the first clinical trial is strongly significant. Suppose that we are interested in testing the following hypotheses:

H_o : the study is not positive versus H_a : the study is positive.

The null hypothesis H_0 is rejected if and only if |T|>c, where c is a positive known constant and T is a test statistic. Thus, the reproducibility probability of observing a significant clinical result when H_a is indeed true is given by

$$p = P(|T| > c \mid H_a) = P(|T| > c| \hat{\theta}),$$

where $\hat{\theta}$ is an estimate of θ, which is an unknown parameter or vector of parameters.

Biosimilarity Index

Following Shao and Chow [12]'s idea, a reproducibility probability can also be used to evaluate biosimilarity and interchangeability between a test product and a reference product based on any pre-specified criteria for biosimilarity and interchangeability. As an example, biosimilarity index proposed by Chow et al. [13] is illustrated based on the well-established bioequivalence criterion by the following steps (see also, Chow, 2013):

Step 1: Assess average biosimilarity based on a given criterion, e.g. (80%, 125%) based on log-transformed data;

Step 2: Calculate the local biosimilarity index (i.e., reproducibility) based on the observed ratio and variability;

Step 3: Claim local biosimilarity if the 95% confidence lower bound of the biosimilarity index is larger than p_0, a pre-specified number.

Note that in practice, P_0 can be obtained based on an estimated of reproducibility probability for a study comparing a reference product to itself (the reference product). We will refer to such a study as an R-R study (see, e.g., Chow, 2013).

To address the totality-of-the-evidence, the following *totality biosimilarity index* derived based on biosimilarity index from each domain proposed by Chow et al. [13] and Chow (2013) may be useful. At each domain, biosimilarity index can be obtained by the following steps:

Step 1: Obtain p_i , the biosimilarity index for the *i* th domain;
Step 2: Define the totality biosimilarity index as $p_T = \sum_{i=1}^{k} w_i p_i$, where w_i is the weight for the *i* th domain, where $i = 1,\ldots,k$ (number of domains);
Step 3: Claim biosimilarity if the 95% confidence lower bound of p_T is greater than a pre-specified p_{T_0} value.
Similar to biosimilarity index, p_{T_0} can be determined based on an estimated of totality biosimilarity index for studies comparing a reference product to itself (the reference product).

The above described biosimilarity index or totality biosimilarity index has the advantages that (i) it is robust with respect to the selected study endpoint, biosimilarity criteria, and study design, (ii) it takes variability into consideration (one of the major criticisms in the assessment of average bioequivalence), (iii) it allows the definition and assessment the degree of similarity (in other words, it provides partial answer to the question that "how similar is considered similar?") and (iv) the use of biosimilarity index or totality biosimilarity index will reflect the sensitivity of heterogeneity in variance.

Switching Index (SI):

Similar idea can be applied to develop switching index under an appropriate study design. For example, under a 4×2 Balaam's crossover design, in order to assess switching, biosimilarity for "R to T", "T to R", "T to T", and "R to R" need to be assessed. Define p_{Ti} the totality biosimilarity index for the ith switch, where =1 (switch from R to R), 2 (switch from T to T), 3 (switch from R to T), and 4 (switch from T to R). As a result, the switching index (SI) can be obtained as follows:

Step 1: Obtain P_{Ti} , *i* = 1, ..., 4*;*

Step 2: Define switching index as $SI = \max_i \left\{ P_{Ti} \right\}$, *i*=1,...,4*,* which is the largest order of the biosimilarity indexes;

Step 3: Claim switchability if the 95% confidence lower bound of *SI* is greater than a pre-specified value P_{s0} .

To obtain the estimates of expectation and variance of *SI* , the sample mean and sample variance of the observations P_{T1} , P_{T2} , …, P_{T4} could be used to replace μ and σ^2 , respectively (see, e.g., Chow 2013). As the result, the 95% confidence low bound of *SI* can be obtained. We then claim switching if the 95% confidence low bound for *SI* is greater than P_{s0}

Alternating Index (AI):

Similar idea can be applied to develop switching index under an appropriate study design. For example, under a modified Balaam's crossover design, i.e., (TT, RR, TRT, RTR), to assess alternating, biosimilarity for "R to T to R" and "T to R to T" need to be assessed. Define p_{Ti} the totality biosimilarity index for the *i* th switch, where *i* =1 (switch from R to R), 2 (switch from T to T), 3 (switch from R to T), and 4 (switch from T to R). As a result, the alternating index (AI) can be obtained as follows:

Step 1: Obtain P_{Ti}, *i* =1,...,4 ;

Step 2: Define the range of these indexes, $AI = \max_i \{p_{Ti}\} - \min_i \{p_{Ti}\}$ for, $i = 1,\ldots,4$ as the alternating index;

Step 3: Claim alternation if the 95% confidence lower bound of *AI* is greater than a pre-specified value P_{A0}

The estimates of expected values and variance of *AI* could be similarly obtained following the process of the confidence lower bound of *SI* . We could estimate μ and σ^2 by the sample mean and sample variance in order to construct the confidence lower bound for *AI*. Thus, we then claim switching if the 95% confidence lower bound for *AI* is greater than p_{A0} . Therefore, we may claim interchangeability if both switching and alternation are concluded.

4 Challenging Issues in Drug Interchangeability

4.1 Modified Large Sample Method for PBE/IBE

Both criteria for PBE and IBE are aggregated moment-based criteria which involve several variance components. Since the criteria are non-linear functions of the direct drug effect, inter-subject and intra-subject variabilities for the test product and the reference product, and the variability due to subject-by-drug interaction, a typical approach is to linearize the criteria and then apply a modified large sample (MLS) method for obtaining an approximate 95% upper confidence bound of the linearized criteria. The key is to decompose the linearized criteria into independent and unbiased estimators so that the MLS or extended MLS methods can be used for obtaining a valid approximate upper confidence bound. In practice, however, the lack of an exact confidence interval for a general linear combination of variance components spurred the development of a modified large-sample (MLS) method commonly occur.

Lee Y et al. [14] considered the problem of setting a confidence interval or bound for a linear combination of variance components related to a multivariate normal distribution, which includes important applications such as comparing variance components and testing the bioequivalence between two drug products. The lack of an exact confidence interval for a general linear combination of variance components spurred the development of a modified large-sample (MLS) method that was shown to be superior to many other approximation methods. But existing MLS method requires the use of independent estimators of variance components. Using a chi-squared representation of a quadratic form of a multivariate normal vector, we extend the MLS method to situations in which estimators of variance components are dependent. Using Edgeworth and Cornish-Fisher expansions, we explicitly derive the second-order asymptotic coverage error of the MLS confidence bound. Our results show that the MLS confidence bound is not second-order accurate in general, but is much better than the confidence bound based on normal approximation and is nearly second-order accurate in some special cases. Lee Y. et al. [14]'s results also show how to construct an MLS confidence bound that is second-order accurate, which is useful for assessment of PBE/IBE.

4.2 Definition of Interchangeable Biosimilar Product

Intuitively, if a test product is judged to be interchangeable with the reference product then it may be substituted, even alternated, without a possible

intervention, or even notification, of the health care provider. However, the interchangeability is expected to produce the *same* clinical result in *any given patient*, which can be interpreted as that the same clinical result can be expected in *every single patient*. In reality, conceivably, lawsuits may be filed if adverse effects are recorded in a patient after switching from one product to another.

In practice, it is often difficult (if not impossible) to demonstrate that a proposed interchangeable biosimilar product can produce the same clinical result as the reference product in any given patient. In other words, for every patient, we need to demonstrate that the proposed interchangeable biosimilar product will produce the same clinical result as the reference product before interchangeability between the biosimilar and reference products can be claimed. However, statistically, it is possible to demonstrate that the proposed biosimilar product can produce the same clinical result as the reference product in any given patient *with certain assurance*. In this case, the concept of individual bioequivalence (IBE) for addressing drug switchability proposed by the FDA in early 2000 may be useful. This is because the assessment of IBE will evaluate not only the difference in treatment effect within each individual but also the effect due to subject-by-treatment interaction, which is known to affect drug interchangeability.

5. Concluding Remarks

Between 1990 and 2000, PBE and IBE were proposed to address drug prescribability and drug switchability for generic drugs. Both PBE and IBE are developed based on aggregated criteria which take mean responses, both inter- and intra-subject variabilities, and the variability due to subject-by-formulation interaction of both test and reference products into consideration. Under aggregated criteria, combinations of different values of means and variances of both test and reference products can yield the same value. In other words, BE can be reached by two totally different distributions of PK metrics. At a 1996 Advisory Committee meeting, it was reported that a decrease in the average is offset by a 48% difference in variability and the product passes IBE but fails ABE [see also, 15,16]. This masking effect has limited the use of PBE/IBE for assessing drug prescribability and drug switchability of generic drugs. It should be noted that the passage of ABE does not guarantee the passage of PBE or IBE and vice versa due to the masking effect of the aggregated criteria of PBE and IBE.

The biosimilarity index proposed by Chow et al. [13] for assessment of biosimilarity and switching/alternation index for addressing drug interchangeability of biosimilar products have the advantages that (i) they can be applied regardless of the criteria for biosimilarity and study design used, (ii) the assessment is made based on the relative difference with the reference, (iii) it can address the commonly asked question that "how similar is considered highly similar?", "the degree of similarity", and "interchangeability in terms of switching and alternating", and most importantly (iv)the proposed method is in compliance with current regulatory thinking.

References

1. FDA. Guidance on Bioavailability and Bioequivalence Studies for Orally Administrated Drug Products - General Considerations. Center for Drug Evaluation and Research, the United States Food and Drug Administration, Rockville, Maryland. 2003.

2. FDA. Guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. The United States Food and Drug Administration, Silver Spring, Maryland. 2015.

3. Chow SC, Liu JP. Current issues in bioequivalence trials. Drug Information Journal. 1995, 29: 795-804.

4. Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. Chapman and Hall/CRC Press, Taylor & Francis. 2008.

5. Chow S, Song F, Cui C. On hybrid parallel–crossover designs for assessing drug interchangeability of biosimilar products. J Biopharm Stat, 2017. 27: 265-271.

6. Endrenyi L, Declerck PJ, Chow SC. Biosimilar drug product development. CRC Press/ Taylor & Francis, London-New York, 2017, 477.

7. FDA. Guidance for Industry - Considerations in Demonstrating Interchangeability with a Reference Product. The United States Food and Drug Administration, Silver Spring, Maryland. 2019.

8. FDA. Guidance on Statistical Approaches for Evaluation of Bioequivalence. Center for Drug Evaluation and Research, the United States Food and Drug Administration, Rockville, Maryland. 2001.

9. Chow SC, Shao J, Wang H. Statistical tests for population bioequivalence. Statistica Sinica. 2003, 13: 539-554.

10. Chow SC, Lee SJ. Design and analysis of biosimilar switching studies. Pharmaceut Med. 2019, 33: 379-388.

11. Chow SC. Biosimilars: Design and Analysis of Follow-on Biologics. Chapman and Hall/CRC, Boca Raton. 2013.

12. Shao J, Chow SC. Reproducibility probability in clinical trials. Stat Med. 2002, 21: 1727-1742.

13. Chow SC, Endrenyi L, Lachenbruch PA, Yang LY, Chi E. Scientific factors for assessing biosimilarity and drug Interchangeability of follow-on Biologics. Biosimilars. 2011, 1: 13-26.

14. Lee Y, Shao J, Chow SC. The modified large sample confidence intervals for linear combinations of variance components: extension, theory and application. Journal of American Statistical Association. 2004, 99: 467-478.

15. Chow SC. Individual bioequivalence - a review of FDA draft guidance. Drug Information Journal. 1999, 33: 435-444.

16. Chow SC, Shao J. Bioequivalence review for drug interchangeability, J Biopharm Stat. 1999, 9: 485-497.

17. BPCI. Biologic Price, Competition, and Innovation Act. United States Congress, Washington DC. 2009.