Journal of
Bioequivalence & Bioavailability
ISSN: 0975-0851

Liu and Chow, J Bioequiv Availab 2015, 7:5
DOI: 10.4172/jbb.1000247

Research Article Open Access

Meta-Analysis for Safety Monitoring of Drug Interchangeability

Wen-Wei Liu* and Shein-Chung Chow

Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA

Abstract

When an innovative (brand-name) drug is going off patent protection, pharmaceutical or generic companies may file an abbreviated new drug application (ANDA) for generic approval. As indicated by the United States Food and Drug Administration (FDA), an approved generic drug can be used as a substitute for the brand-name drug. FDA, however, does not indicate that approved generic drugs of the same brand-name drug can be used interchangeably. As more generic drugs become available in the marketplace, it is a concern whether the approved generic drugs are safe and can be used interchangeably. In this article, we propose two safety margins as new bioequivalence limits for monitoring of drug interchangeability based on a meta-analysis of data obtained from regulatory submissions which have been approved by FDA. In addition to the monitoring of drug interchangeability of generic drugs, the proposed margins can also be extended to address drug interchangeability of biosimilars.

Keywords: Drug interchangeability; Safety margins for safety monitoring; Switchability; Prescribability

Introduction

When an innovative (brand-name) drug is going off patent protection, the innovative drug companies and/or generic drug companies may file an abbreviated new drug application (ANDA) for generic approval through the conduct of a bioequivalence study. Bioequivalence testing for generic approval is based on the Fundamental Bioequivalence Assumption that when two drug products have similar drug absorption profiles (or equivalent in average bioavailability), it is assumed that they will reach similar therapeutic effects or they are therapeutic equivalent. Two drug products are claimed to be bioequivalent if the 90% confidence interval for the geometric mean ratio (GMR) is totally within the bioequivalent limits of (80.00%, 125.00%) based on log-transformed data [1,2]. For an approved generic drug product, the United States Food and Drug Administration (FDA) indicates that it can be used as a substitute of the brand-name drug.

In recent years, as more generic drug products are available in the marketplace, it is a concern whether the approved generic drugs work as well as the brand-name drug in terms of quality and safety. In practice, it is very common that patients may switch from one generic to another depending upon the availability and inexpensiveness of the generic drugs. Thus, it is a concern that such a switch from a generic drug (e.g., approved on the lower end of bioequivalence limit) to another (e.g., approved on the higher end of bioequivalence limit) could cause a drastic change in blood concentration and consequently cause a safety concern. This issue is critical not only for generic drugs of small molecular innovative drugs, but also for biosimilars, which are (large molecular) similar biologic drug products [3].

Biosimilars are the biological drug products that made from living organisms by means of recombinant DNA or controlled gene-expression methods, which is also known as follow-on biologics as indicated by Chow [3], there are fundamental differences between generic drugs and biosimilars (Table 1). As can be seen in Table 1, generic drug products have the well-defined structure and can be characterized, while biosimilars are difficult to characterize due to their heterogeneous and complicated structures with mixtures of various molecules. Thus, generic drug products are usually relatively stable. However, since biosimilars are derived from living cells or organisms, they have the biological property which is variable and sensitive to environmental conditions such as light and temperature. A slight change or variation during the manufacturing process may result different function, efficacy, and safety. In addition, unwanted immune response is the worst result of biosimilars which may cause a loss of efficacy or cause some safety issues.

In this article, safety monitoring procedures based on meta-analysis of data available in approved regulatory submissions (e.g., ANDA for generic approval) is proposed. The proposed margins can be extended to monitoring the safety of drug interchangeability of biosimilar drug products.

Bioequivalence and Drug Interchangeability

Bioequivalence

When the innovative drugs want to get the approval from FDA, the pharmaceutical companies have to file new drug applications (NDA). However, for the generic drugs which are identical to the innovative (brand-name) drugs, they only need to file ANDA which lack the process of animal studies as well as clinical safety and efficacy trials compared to NDA [4]. The United States *Federal Food, Drug, and*

Generic Drug Products	Biosimilars
Made by chemical synthesis	Made by living cells or organisms
Defined structure	Heterogeneous structure Mixtures of related molecules
Easy to characterize	Difficult to characterize
Relatively stable	Variable, and sensitive to environmental conditions, such as light and temperature
No issue of immunogenicity	Issue of immunogenicity
Usually taken orally	Usually injected
Often prescribed by a general practitioner	Usually prescribed by specialists

Table 1: Fundamental differences between generic drug products and biosimilars

***Corresponding author:** Wen-Wei Liu, M.S., Department of Biostatistics and Bioinformatics, Duke University School of Medicine, 2424 Erwin Road, Durham, NC 27705, USA, E-mail: wen-wei.liu@duke.edu

Received June 25, 2015; **Accepted** July 27, 2015; **Published** August 08, 2015

Citation: Liu WW, Chow SC (2015) Meta-Analysis for Safety Monitoring of Drug Interchangeability. J Bioequiv Availab 7: 239-243. doi:10.4172/jbb.1000247

Cosmetic Act (FDCA), enacted by Congress in 1938, gives authority to FDA, and provisions for generic drugs were added in 1984 as *Drug Price Competition and Patent Term Restoration Act*. It states that rate and extent of drug absorption must be compared to establish bioequivalence between two products. Bioavailability of a drug can be described as the extent and rate of the absorption of active drug ingredient from the drug product to the site intended to treat, and it is usually measured by the area under the blood or plasma concentration-time curve (AUC) and the maximum concentration (C_{max}) respectively. The FDA's regulations are codified in Title 21 of the Code of Federal Regulations (21 CFR) which clear defines C_{max} as index of rate of absorption and AUC as index of extent of absorption. If the drug is not absorbed from bloodstream, bioavailability can also be assessed by measurements intended to reflect the extent and rate. A comparative bioavailability study indicates the comparison of bioavailabilities of different formulations of the same drug or different drug products, and they are claimed bioequivalent when assuming that they will provide the same therapeutic effect or that they are therapeutically equivalent.

"If two drug products are shown to be bioequivalent, it is assumed that they will generally reach the same therapeutic effect or they are therapeutically equivalent" stated by Chow and Liu [1] is known as the Fundamental Bioequivalence Assumption, and bioequivalence assess for generic drug approval should be conducted under this assumption. However, there are four possible scenarios in practice and only one indicates this assumption. The second scenario indicates the two drug absorptions profiles are not similar but they are therapeutically equivalent, and this is the case that generic drug companies might argue when their generic products fail to meet regulatory requirements. The third scenario indicates the two drug absorptions profiles are similar but they are actually not therapeutically equivalent, and innovative drug companies usually argue the inefficacy of the generic copies under this scenario. And the forth scenario is the worst one which indicates the two drug absorptions profiles are not similar and they are not therapeutically equivalent. Therefore, Fundamental Bioequivalence Assumption has been criticized that it is not based on scientific considerations.

80/125 Decision rule

There are many decision rules for evaluation of average bioequivalence. The ± 20 rule was applied to assess average bioequivalence in early 1980. During the same time, it was suggested that the 80/20 rule be used as the secondary analysis to support the ± 20 rule. However, since the two rules may result in different conclusions with some possible practical issues, FDA recommended the 80/125 rule be used based on log-transformed data [1].

FDA guidance [2] suggested that the log- transformation on AUC and C_{max} be considered. Thus, if the 90% confidence interval for the average bioequivalence of the test formulation over the reference formulation is within (80.00%, 125.00%), then the bioequivalence can be concluded. The range for the criterion is $ln(0.80) = -0.2231$ to $ln(1.25) = 0.2231$, and it is symmetric about $ln(1.00) = 0$ where the test formulation is totally equivalent to the reference formulation [1].

Drug interchangeability

When the generic drugs get the approvals from FDA, that does not indicate that approved generic drugs and the innovative drugs can be used interchangeably. The FDA only indicates that approved generic drugs can be used as a substitute to the innovative drugs. Drug interchangeability for generic drugs can be classified as prescribability or switchability [5,6]. However, we used average bioequivalence in this study to simplify this problem since it is the usual method to assess the bioequivalence.

Drug prescribability is described as the physician's decision to prescribe the brand-name drug or its generic copies under the condition that they can be used interchangeably in terms of efficacy and safety. If brand-name drug and its generic copies are bioequivalent in both average and variability, it can be claimed *population bioequivalence (PBE)* which usually used to clarify drug prescribability [6]. PBE is usually applied to new formulations, additional strengths, or new dosage forms in NDAs. Drug switchability then is indicated as the exchangeability within the same subject. It can be referred as from brand-name drug to generic copy or from a generic drug to the other generic copies. Drug switchability is ensured by *individual bioequivalence (IBE)* which describes the majority of subjects satisfy the criteria [5]. IBE should be considered for ANDA or AADA (abbreviated antibiotic drug application) for generic drugs. However, there has been debate on the criteria recommended by FDA, so now FDA suggests the method of small sample confidence interval approach proposed by Hyslop et al. be considered for assessment of PBE/IBE for statistical analysis [7].

Meta-Analysis for Safety Monitoring

In general, meta-analysis combines small studies for a systematic review. In practice, the sample sizes of some studies might be relatively small. In addition, some trials may fail to show a statistically significant treatment effects. Thus, by combining these studies, meta-analysis can provide a more accurate and reliable assessment of the treatment effect under investigation.

In order to achieve the ultimate goals of better accuracy and reliability of the treatment effect, the following general principles need to be taken into consideration when performing a meta-analysis.

(1) It is often a concern that only positive clinical studies are included in the meta-analysis, which may have introduced selection bias. To avoid this, criteria for selection of studies and the time period to be included in the meta-analysis need to be clearly stated in the study protocol. If there is a potential trend over time, a statement need to be provided for scientific justification for inclusion of the studies selected.

(2) It is critical to assess similarity and dis-similarity among studies to reduce variability for a more accurate and reliable assessment of the test treatment under investigation because different studies may be conducted with similar but different study protocols, drug products and doses, patient populations, sample sizes, evaluability criteria and so on.

(3) Before the data sets obtained from different studies can be combined for a meta-analysis, it is suggested that a statistical test for poolability be performed to determine whether there is significant treatment-by-study interaction.

Meta-analysis

For each study trial, 90% confidence interval for log-transformed data can be constructed. If it is within (80%, 125%), then bioequivalence is claimed. However, current generic approval criteria based on the average bioequivalence has the limitation that cannot guarantee the drug interchangeability. If any trial has lower bound L* which is lower than L (lower margin) but higher than 80% or the upper bound U* is higher than U (upper margin) but lower than 125%, then it might have the safety concern since the relative change of concentration of the

drug in blood is dramatic. Assume the bioequivalence of the generic drug a patient used for a long period was close to 125%, and now a physician switches to another generic drug which with bioequivalence close to 80%. We may wonder if the new generic drug can still be used to heal the patient as efficient as the old one because the concentration of the drug in blood decreases (125-80)/125=36% to the original. Correspondingly, the concentration of the drug in blood may also increases (|80-125|)/80=56% to the original. By doing the meta-analysis in different clinical trials for the same brand-name drug, we will have several margins as the monitoring tool to evaluate all generic drugs and calculate $P(L^*<L)$ and $P(U^*>U)$ as the probability of the improper rate.

From the previous study by Chow and Liu [8], a meta-analysis for a systemic overview of bioequivalence was proposed. Suppose there are K different trials for the same brand-name drug. Follow the assumptions below:

(1) The same standard two-sequence, two-period crossover design was constructed with n_{k1} and n_{k2} at sequence 1 and 2, where $k = 1,\ldots, K$.

(2) The same statistical model was used for log-transformed data to assess bioequivalence.

(3) Inter-subject variabilities are the same for all subjects. ($\sigma_{sk}^2 = \sigma_s^2$ for all k.)

(4) Intra-subject variabilities are the same for all subjects. ($\sigma_{ek}^2 = \sigma_e^2$ for all k.)

To combine the data from the K studies, we first test for the homogeneity of the reference products among the studies. We can derive the following chi-square distribution with K-1 degrees of freedom to test homogeneity.

$$\chi_R^2 = \sum_{k=1}^{K} \frac{1}{C_k}\left(\bar{Y}_{Rk} - \hat{\mu}_R\right)^2$$

Where $C_k = \frac{1}{4}\left(\frac{1}{n_{k1}} + \frac{1}{n_{k2}}\right)$ and $\hat{\mu}_R = \sum_{k=1}^{K}\left(\frac{\frac{1}{C_k\left(\sigma_e^2+\sigma_S^2\right)}\bar{Y}_{Rk}}{\sum_{k=1}^{K}\frac{1}{C_k\left(\sigma_e^2+\sigma_S^2\right)}}\right) = \sum_{k=1}^{K}\left(\frac{\frac{1}{C_k}\bar{Y}_{Rk}}{\sum_{k=1}^{K}\frac{1}{C_k}}\right)$

Reject the null hypothesis of homogeneity at the α level of significance if

$$\chi_R^2 > \chi^2\left(\alpha, K-1\right)$$

If we fail to reject the null hypothesis of homogeneity, we can combine drug effect and get the corresponding confidence intervals. Let

$$\hat{d}_k = \bar{Y}_{Tk} - \bar{Y}_{Rk}, k = 1,\ldots,K,$$

be the difference of the least squares means between the test product and the reference product of the k^{th} study. If we assume that μ_{Tk}, k=1, ..., K, are the same for all studies ($\mu_{Tk} = \mu_T$ for all k), a combined estimate for $\mu_T - \mu_R$ is the weighted means of $\hat{d}_k$, i.e.,

$$\bar{d} = \sum_{k=1}^{K}\left(\frac{\frac{1}{C_k}\bar{d}_k}{\sum_{k=1}^{K}\frac{1}{C_k}}\right), \text{where } Var\left(\bar{d}\right) = = \left(\frac{\sigma_e^2}{\sum_{k=1}^{K}\frac{1}{C_k}}\right)$$

Then a (1-2α)x100% confidence interval, denoted by (L_m, U_m), can be obtained as follows:

$$\left(L_m, U_m\right) = \bar{d} \pm t\left(\alpha, \sum_{k=1}^{K}\left(n_{k1} - n_{k2} - 2\right)\right)\sqrt{\hat{V}\left(\bar{d}\right)}$$

Safety Margins for Monitoring Drug Interchangeability and Simulation Study

The studies in meta-analysis are all approved generic drugs, so the 90% confidence intervals are all located within (80%, 125%). However, as described in "Meta-analysis", it might have some concerns while switching from one generic drug to another. Therefore, safety margin for interchangeability cannot use (80%, 125%), and if applying (L_m, U_m), drug concentration in blood will not change so much, so it could be selected as a margin. However, it is too narrow and strict, for example, (L_m, U_m) = (95%, 105%) so I proposed several margins to monitor the drug interchangeability. The hypothesis can be expressed as following:

$$H_0: \frac{(|L-U|)}{L} \le \tau \text{ and } \frac{(U-L)}{L} \le \tau \text{ vs. } H_1: \frac{(|L-U|)}{L} > \tau \text{ or } \frac{(U-L)}{L} > \tau$$

Safety margins for monitoring drug interchangeability

Margin 1 (M1): Let (L_m, U_m) be the 90% confidence interval obtained from a meta-analysis. Set $L_1=L_m-\delta_L$ and $U_1=U_m-\delta_M$, where $\delta_L=(L_m-0.8)/2$ and $\delta_M=(1.25-U_m)/2$. Actually, L_1 is in the middle of 0.8 and L_m, and U_1 is in the middle of 1.25 and U_m. (L_1, U_1) is our first set of margins.

Margin 2 (M2): For each meta-analysis, we can get the lower margin (L) which is smaller than 95% of the lower bounds (L^*) from the 90% C.I. of different studies, and it can be expressed as $P(L^* \ge L_2) = 95\%$. Correspondingly, the upper margin (U) is larger than 95% of the upper bound (U^*) from the 90% C.I. of different studies, and it can be expressed as $P(U^* \le U_2) = 95\%$. Therefore, L_2 will be like the 5th percentile of the boundaries, and U_2 will be the 95th percentile of the boundaries. Since we will simulate 20 dataset for a meta-analysis, L_2 is the second smallest lower bound, and U_2 is the second largest upper bound.

Margin 3 (M3) and **Margin 4 (M4)** are similar to **Margin 2 (M2)** but with different probability. For Margin3, it is $P(L^* \ge L_3) = 90\%$, $P(U^* \ge U_3) = 90\%$. For Margin4, it is $P(L^* \ge L_4) = 85\%$, $P(U^* \ge U_4) = 85\%$ (Figure 1).

Simulation study

All the studies in meta-analysis are approved generic drugs, so the data is regulated by FDA and we cannot get these real data. Therefore, the simulation study is conducted. In this study, we simulate 24 subjects in a dataset and 20 dataset as 1 meta-analysis study, and we simulate 1,000 meta-analysis studies from one scenario. There are 6 scenarios in this study (Table 2). For each scenario, there is the average meta-analysis 90% confidence interval derived by the formula in "Meta-analysis" (Table 3). The margins (M1~M4) for each scenario (S1~S6) can also be obtained by the definition in Section4.1. The probability of the 90% C.I. for a study below the lower margin (Below L), or above the upper margin (Above U) can be calculated. Safety impact is when the efficacy of original drug is close to the lower margin and suddenly changes to the drug with efficacy close to the upper margin, which is

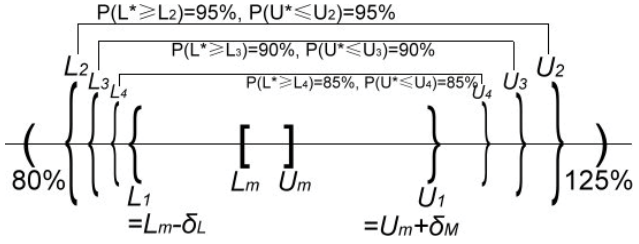

Figure 1: Relationships among BE limits, meta-analysis confidence limits, Margin1, Margin2, Margin3 and Margin4.

Scenarios	S1	S2	S3	S4	S5	S6
μ	100	100	100	105	105	105
$\sigma_s = \sigma_e$	10	20	30	10	20	30

Table 2. Parameter specification for the simulation studies.

calculated as $\frac{(|L-U|)}{L}$ (Low to High), correspondingly, efficacy impact is calculate as $\frac{(U-L)}{U}$ (High to Low).

The 90% confidence interval obtained from meta-analysis is usually narrower than the confidence interval from one study, so we adjust it by δ. From Table 3, we can see the confidence intervals are similar when the true variances (σ_s^2, σ_e^2) are the same, and they get larger when the true variances become larger. In addition, the probability of the confidence interval for a study lower than the lower margin (Below L), or higher than the upper margin (Above U) are all 0.050 for margin2 (M2), 0.100 for margin3 (M3) and 0.150 for margin4 (M4) since it is the definition for these margins. However, the Safety/Efficacy Impact seems to be smaller when the true mean (μ) is larger. And it is not surprising that when the true variance gets larger, the Safety/Efficacy Impact also gets larger. In addition, the Below L and Above U have the same situation as the Safety/Efficacy Impact, and they dramatically increase for margin1 (M1) when variance gets larger. Margin1, margin2, margin3 and margin4 are similar when variances are small. However, when variances get larger, they perform differently and margin1 is usually the narrowest one. From regulatory point of view, if we choose the criterion for Safety/Efficacy Impact is 30%, that is τ= 0.3 in the hypothesis, then we can see when the variance is small, all margins can meet this criterion. However, the variance in real data is usually located between 20 and 30, and we can see only margin1 meets this criterion. Therefore, proposed Margin1 is a useful tool for safety monitoring for interchangeability.

Application to Biosimilars

The basic concept of statistical method used to assess bioequivalence for generic drugs and biosimilarity for biosimilars are consistent (ex. the 80/125 decision rule), so we could apply the results in this study to biosimilars. Europe, generic versions of biological drug products are administrated by European Medicines Agency (EMA), and are defined as a "version of an already authorized biological medicinal product with demonstrated similarity in quality characteristics, biological activity, efficacy and safety, based on a comprehensive comparability exercise" [9]. They have issued several guidelines describing overarching and specific biosimilar. In the United State, the current approval for generic versions of biological drug products is based on *Biologics Price Competition and Innovation (BPCI) Act*, which was originally sponsored and introduced on June 26, 2007 by Senator Edward Kennedy (D-MA) and written into law on March 23, 2010. As indicated in the *BPCI Act*, a biosimilar product is defined as a product that is "highly similar" to an already-approved biological product clinically in terms of safety, purity, and potency, notwithstanding minor differences in clinically inactive components. Here purity may be related to some important quality attributes at critical stages of the manufacturing process, and potency has something to do with the stability and efficacy of the biosimilar product.

The BPCI Act seems to suggest that a biosimilar product should be highly similar (sufficiently close) to the reference drug product in all spectrums of good drug characteristics such as identity, strength (potency), quality, purity, safety, and stability as described in the United States Pharmacopeia and National Formulary (USP/NF). In addition, FDA draft guidance [10] suggests "stepwise approach" and the concept of "totality-of-the-evidence." This indicates that the FDA is interested in demonstrating global similarity in all aspects related to safety, purity, and potency of the biosimilar products, but it is almost impossible to demonstrate that a biosimilar product is highly similar to the reference product in all aspects of good drug characteristics in a single study. Thus, to ensure that a biosimilar product is highly similar to the reference product in terms of these good drug characteristics, biosimilar studies for different aims may be required. For example, if safety and efficacy are the concern, then a clinical trial must be conducted to demonstrate that there are no clinically meaningful differences in terms of safety and efficacy between a biosimilar product and the innovator biological product. On the other hand, to ensure that important quality attributes are highly similar, critical stages of the manufacturing process, assay development/validation, process control/validation, and product specification of the reference product should be necessarily established through the conduct of relevant studies.

Similar to the Fundamental Bioequivalence Assumption, Chow et al. [11] proposed the following Fundamental Biosimilarity Assumption for follow-on biologics: *When a biosimilar product is claimed to be biosimilar to an innovator's product based on some well-defined product characteristics, it is therapeutically equivalent, provided that the well-defined product characteristics are validated and are reliable predictors of safety and efficacy of the products.* Unlike the Fundamental Bioequivalence Assumption assumes that equivalence in the exposure measures implies therapeutical equivalence, Fundamental Biosimilarity Assumption has to verify that some validated product characteristics are indeed reliable predictors of safety and efficacy.

However, generic drugs and biosimilars are slightly different in drug interchangeability. As indicated in the subsection (k)(4) amends the *Public Health Act subsection 351(k)(4)*, of the *BPCI Act*, the term interchangeable or interchangeability in reference to a biological product, means that the biological product may be biosimilar to the reference product and expected to produce the same clinical result in any given patient. In addition, the biological product may also be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. However, unlike the interchangeability of small-molecule drug products, which could be described as prescribability and switchability, the FDA considers interchangeability includes the concepts of switching and alternating between an innovative biologic product (R) and its biosimilars (T). The concept of switching involves the switch from not only "R to T" or "T to R" but also "T to T" and "R to R." As a result, in order to assess switching, biosimilarity for "R to T," "T to R," "T to T," and "R to R" needs to be assessed based on some biosimilarity criteria under a valid study design.

On the other hand, the concept of alternating is referred to as either 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" or "the switch from R to T" and "the switch from R to T" or "the switch from T to R" needs to be assessed for addressing the concept of alternating.

Concluding Remarks

The concept of drug interchangeability for generic (small molecule) drug products and biosimilars (generic versions of large molecule biological drug products) is similar but different, so the interpretation should be carefully handled. Based on the 80/125 rule, it is not usual

						Safety/Efficacy Impact	
		(L_m, U_m)	(L, U)	Below L	Above U	Low to High	High to Low
S1	M1	(0.991,1.012)	(0.896,1.131)	0.178	0.104	0.263	0.208
	M2		(0.882,1.135)	0.050	0.050	0.287	0.223
	M3		(0.892,1.121)	0.100	0.100	0.258	0.205
	M4		(0.900,1.111)	0.150	0.150	0.235	0.190
S2	M1	(0.981,1.024)	(0.891,1.137)	0.649	0.586	0.277	0.217
	M2		(0.814,1.228)	0.050	0.050	0.508	0.337
	M3		(0.821,1.218)	0.100	0.100	0.484	0.326
	M4		(0.827,1.208)	0.150	0.150	0.461	0.315
S3	M1	(0.973,1.027)	(0.887,1.139)	0.909	0.877	0.284	0.221
	M2		(0.805,1.242)	0.050	0.050	0.543	0.352
	M3		(0.808,1.238)	0.100	0.100	0.532	0.347
	M4		(0.811,1.234)	0.150	0.150	0.522	0.343
S4	M1	(0.990,1.010)	(0.895,1.130)	0.143	0.082	0.263	0.208
	M2		(0.888,1.126)	0.050	0.050	0.269	0.212
	M3		(0.897,1.114)	0.100	0.100	0.242	0.194
	M4		(0.905,1.105)	0.150	0.150	0.222	0.181
S5	M1	(0.983,1.024)	(0.892,1.137)	0.614	0.541	0.276	0.216
	M2		(0.816,1.224)	0.050	0.050	0.500	0.333
	M3		(0.824,1.213)	0.100	0.100	0.473	0.321
	M4		(0.831,1.202)	0.150	0.150	0.446	0.308
S6	M1	(0.972,1.025)	(0.886,1.138)	0.889	0.860	0.284	0.221
	M2		(0.806,1.241)	0.050	0.050	0.541	0.351
	M3		(0.809,1.236)	0.100	0.100	0.529	0.346
	M4		(0.812,1.232)	0.150	0.150	0.518	0.341

Table 3. Safety and efficacy margin for interchangeability

but possible to cause the dramatic change of the concentration of drug in blood if changing one drug to another. And this change may cause the uncertainty of the safety or efficacy. Based on the margins proposed in this study, margin1 has better ability to control safety and efficacy impact so we can say it is a useful tool for safety monitoring for interchangeability. However, it has higher probability of the confidence interval for a study below the lower margin (Below L), or above the upper margin (Above U) indicates that if we set this margin as the new criteria rule rather than (80%, 125%), there will be so many bioequivalence/biosimilar studies that do not meet this criterion. Therefore, drug interchangeability for bioequivalence/biosimilar is a big issue and we can do the future work to interpret this by using mathematical formula.

References

1. Chow SC, Liu JP (2008) Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd (Edn), Chapman Hall/CRC Press, Taylor & Francis, New York.
2. FDA (2003) Guidance on Bioavailability and Bioequivalence Studies for Orally Administrated Drug Products - General Considerations. Rockville, Maryland.
3. Chow SC (2013) Biosimilars: Design and Analysis of Follow-on Biologics. 1st (Edn), Chapman Hall/CRC Press, Taylor & Francis, New York.
4. Chow SC (2014) Bioavailability and Bioequivalence in Drug Development. Wiley Interdiscip Rev Comput Stat 6: 304-312.
5. Chow SC, Shao J, Wang H (2002) Individual bioequivalence testing under 2x3 designs. Stat Med 21: 629-648.
6. Chow SC, Shao J, Wang HS (2003) Statistical tests for population bioequivalence. Statistica Sinica 13: 539-554.
7. Hyslop T, Hsuan F, Holder DJ (2000) A small sample confidence interval approach to assess individual bioequivalence. Stat Med 19: 2885-2897.
8. Chow SC, Liu JP (1997) Meta-analysis for bioequivalence review. J Biopharm Stat 7: 97-111.
9. EMA (2014) Guideline on Similar Biological Medicinal Products. Canary Wharf, London, UK.
10. FDA (2015) Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. Silver Spring, Maryland.
11. Chow SC, Lu Q, Tse SK, Chi E (2010) Statistical methods for assessment of biosimilarity using biomarker data. J Biopharm Stat 20: 90-105.