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Statistical Designs for Assessing Interchangeability of Biosimilar Products

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Abstract

More and more biopharmaceutical and/or biotech companies begin to concern regulatory approval of biosimilar products, due to some innovator products will expire in decades. Once more biological products are going off patient, the problem whether approving biosimilar products used interchangeably and safely will be considered. Using a biological product of the reference product interchangeably, the United States Food and Drug Administration (FDA) requires that, 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. For this purpose, based on the concept of switching and/or alternation several useful designs for assessing drug interchangeability are proposed. In addition, by developed biosimilarity index, a unified approach is discussed. The proposed method is robust against biosimilarity criteria and is applicable under a valid and appropriate study design.

Keywords: Biosimilarity index; Switching, Alternation; Balaam's design; Two-sequence dual design; Williams design

Introduction

When the patent of the brand-name drug product expires, generic companies and/or bio- pharmaceutical have to file an Abbreviated New Drug Application (ANDA) for generic approval. Under Fundamental Bioequivalence Assumption, when a generic drug is claimed to be bioequivalent to a brand-name drug, it is assumed that they are therapeutically equivalent [1]. If it has been shown to be bioequivalent to the brand-name drugs, a generic drug is generally is an alternative to brand name drugs. FDA [2] does not indicate the two generic versions of the same brand-name drug may be used interchangeably, even though they are proved to bioequivalent to the same brand-name drug. Factually, bioequivalence is not required between the two generic versions of a same brand-name drug. However, as each of generic drug products is bioequivalent to the innovative products, we will concern whether the approved generic drug products have mutually the same quality and therapeutic effect, and whether they can be used safely and interchangeably. The concept of drug interchangeability includes two facets: drug prescribability and drug switchability. Drug prescribability is that physician prescribes an appropriate drug for the patients by choosing the brand-name drug or its generic copies, while drug switchability is referred that under a steady, efficacious and safe condition, the same patient is administered a drug, from a drug (e.g., a brand-name drug or its generic copies) switching to another (e.g., a generic copy). To ensure that generic drug products can be administered interchangeably and safely, the FDA suggested that the population and individual bioequivalence of approved generic drug products should be evaluated [2-5].

Since the patents of some innovative drug products expire in the coming years and biosimilar manufacturers compete for a part of the already large and fast-growing market, the subsequent production of these biosimilar products have been concerned in the biotech industry/pharmaceutical. Even though the innovative biologic products play a main role, the slightly cheaper price of for the generic drugs outweighs the increased risk of side-effects; potential opportunity for price reduction is coming. Thus, it is a great concern to prove whether the approved biosimilar products could be used interchangeably and safely.

In the section of Interchangeability for Biosimilar Products, the definition, interpretation, and assessment of interchangeability for biosimilars are given from two ways: switching and alternating, as described in the Biologics Price Competition and Innovation Act (BPCI) [6] (as part of the Affordable Care Act). Several study designs for addressing switching, alternating, and/or switching/alternating are summarized in the section of Designs for Interchangeability. In the section of statistical methods which is based on the concept of reproducibility probability [7], a general unified approach for the assessment of biosimilarity and interchangeability is outlined by biosimilarity index.

Interchangeability for Biosimilar Products

As depicted in the Public Health Act Subsection 551(k) (FDA [7]), the interchangeable product or interchangeability is referred to meet the standards in subsection (k)(4) (i.e., interchangeability), that is, regardless of the intervention of the health provider who prescribes the innovative product, biological product may replace to the reference product. In what follows, we will introduce the definition and basic concepts of interchangeability in terms of switching and alternation.

Definition and basic concepts

As indicated in the Public Health Act Subsection 351(k)(3), 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, consideration of the safety or efficacy of switching or alternating, when a biological product is used more than

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once to an individual, the risk of alternating or switching between the biological product and the reference product is not greater than the risk without such alternation or switching. As a result, biosimilarity is different from interchangeability; the latter is much more stringent.

As indicated in the Public Health Act subsection 351(k)(3), 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, consideration of the safety or efficacy of switching or alternating, when a biological product is used more than once to an individual, the risk of alternating or switching between the biological product and the reference product is not greater than the risk without such alternation or switching.

It should be pointed out that biosimilarity is proved by the average bioequivalence (ABE), population bioequivalence (PBE) and individual bioequivalence (IBE) on some biosimilar criteria between the generic drug and the reference product. The claim of biosimilarity by FDA doesn't mean these products to be interchangeable. Therefore, the label should indicate whether the generic drug has or has not been proved to be interchangeable with a reference product. However though interchangeability has not been approved, in some cases, switching products could be happened.

Switching and alternation

Unlike drug interchangeability is referred in Chow and Liu [1] (including prescribability and switchability), the U.S. FDA has slight perception for drug interchangeability between biosimilar products. From the FDA's standpoint, interchangeability is considered by switching and alternating between the reference/brand-name product (R) and its generic/test product (T). In narrow sense switching is referred to change from "R to T" or "T to R", and in broader sense it also is switched such as "T to T" and "R to R". Note that "T to T" could indicate a switch from an approved biosimilar product to another approved biosimilar product, while "R to R" could be a switch from an innovative product to itself (e.g., from a different batch or made at a different location). Under a valid study design, for evaluating the switching between the two products such as "R to T", "T to R", "T to T", and "R to R", biosimilarity needs to be assessed under the biosimilarity criteria. The BPCI Act points out that in sense of safety or decreasing efficacy, the risk of switching between the generic product and the innovative product, should not be greater than the risk of no switch. Denoting T*i*, *i*=1, .., K, be the possible biosimilar product, where K is the number of biosimilars, it is suggested that the risk of switching between the biosimilars Ti and R, should be equal or less than the risk of switching between R and R.

The concept of alternating is referred to as a 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"). It only involves one test product T and one reference product R. Thus, in order to address the concept of alternation, the difference of the two switches ("RT R" and "T RT") mentioned above need to be assessed. Concerning safety or diminished efficacy of alternation, BPCI Act also indicates that the risk of alternating between test product and the reference product, should equal or less than the risk without such alternating. In practice, we notice that there may be more than one test product on the market, thus, several switches are possible, e.g., R to T1 to T2 to R to T2, etc. which makes the assessment of alternation even more complicated if it is not impossible.

Thus, in practice, it is not easy, if not impossible; to assess drug interchangeability of approved biosimilar products especially there are multiple T's and R's in the market place. As stated in the BPCI Act, the relative risk between switching/alternating and without switching/alternating must be evaluated. However, little or no discussion about the assessing criteria of the relative risk is mentioned in the BPCI Act. In the recent FDA draft guidances on the demonstration of biosimilarity between biosimilars, there is little or no the criteria, study designs are involved to, neither statistical methods of assessing drug interchangeability are described. Thus, detailed regulatory guidances regarding the assessment of drug interchangeability need to be developed in terms of switching and/or alternating.

For assessing drug interchangeability, in terms of safety or diminished efficacy, an appropriate study design should be chosen to address (i) the risk of alternating or switching between the uses of the generic product and the innovative product, (ii) the risk of using the reference product without alternation or switching, and (iii) the relative risk between switching/alternating and without switching/alternating.

In order to evaluate switching, an appropriate study design should allow the assessment of biosimilarity for "R to T", "T to R", "T to T", and "R to R", and evaluate the risks of switching and no switching, and the relative risk between them. In this case, it is reasonable to use the Balaam's 4×2 crossover design, (i.e., T T, RR, T R, RT); the corresponding risk of switching from "T to T", "R to R", "T to R" and "R to T" can be assessed under a Balaam's design, at the same time the relative risk can be obtained.

Remarks

Generally, the therapeutic equivalence can be reflected by bioequivalence for small molecule drug products, and drug prescribability, switching and alternating can be considered reasonably. For biologic products, they often have larger variation due to sensitivity to small changes in conditions. Thus, parallel design often is prior to crossover kinetic studies chosen. But it is noticeable that the biosimilarity does not illustrate the therapeutic comparability. Provided that clearly regulatory guidances on criteria, design and analysis are available, switching and alternating should be considered with substantial caution.

Designs for Interchangeability

For the chemical drug product without relatively long half-lives, it often recommends a standard two-sequence, two-period (2×2) crossover design to assess bioequivalence. However, a parallel design is often chosen for most biosimilar products because of their relatively long half-lives, but dependent estimates of variance components may be limited, including inter- and intra-subject variabilities and variability due to subject-by-product interaction. Thus, it is a major challenge for assessment of biosimilarity (especially drug interchangeability) under a parallel group design because each patient will be administered the same product once.

As indicated in the BPCI Act, if a biological product is administered to an individual more than once, switching or alternating will be happened between the biological product and the reference product, in terms of safety or diminished efficacy the risk of alternating or switching is not greater than the risk of only using the reference product without any switching or alternating. Thus, for assessing drug interchangeability, an appropriate study design should be chosen. In the following section, we will discuss several useful designs for addressing switching and alternating of biosimilar products.

Designs for switching

Under the broader sense of switchability, it includes (1) switch from "R to T", (2) switch from "T to R", (3) switch from "T to T", and (4) switch to "R to R". Thus, based on some biosimilarity criteria in order to assess interchangeability of switching, a valid study design should be found to assess biosimilarity of the four cases mentioned above. For this purpose, the following study designs are considered.

Balaam's design: Balaam's design is a 4×2 crossover design, denoted by T T, RR, T R, and RT respectively. Under a 4×2 Balaam's design, qualified subjects will be assigned to receive one of the four treatment sequences randomly. For example, subjects in sequence 3 of T R will receive the biosimilar product first and then crossover to the innovative biological product after a sufficient length of washout. In practice, a Balaam's design combines a parallel design (the first two sequences) and a crossover design (sequences #3 and #4). The purpose of the part of parallel design is to obtain independent estimates of intra-subject variabilities for the biosimilar product and the innovative product. In the interest of assigning more subjects to the crossover phase, an unequal treatment assignment is usually employed. For example, we may consider a 1:2 allocation to the parallel phase and the crossover phase. In this case, for a sample size of N=24, to assign 8 subjects to the parallel phase and 16 subjects to the crossover phase. As a result, 4 subjects will be assigned to sequences #1 and #2, respectively, while 8 subjects will be assigned to sequence #3 and #4 respectively, presuming that there is a 1:1 ratio treatment allocation within each phase.

From Table 1, the first sequence provides independent estimate of the intra-subject variability of the biosimilar product, and the assessment for "switch from T to T". Similarly the second sequence provides independent estimate of the intra-subject variability of the innovative product and compares difference between "R and R". The other two sequences assess similarity for "switch from T to R" and "switch from R to T", respectively. Under the 4×2 Balaam design, the following comparisons are usually assessed:

(1) Comparisons by sequence;

(2) Comparisons by period;

(3) T vs R based on sequence #3 and #4 this is equivalent to a typical 2×2 crossover design;

(4) T vs R given T based on sequence #1 and #3;

(5) R vs T given R based on sequence #2 and #4;

(6) The comparison between (1) and (3) for assessment of treatment-by-period interaction.

It should be pointed out that the interpretations of the above comparisons are different. More information regarding statistical methods for data analysis of Balaam's design can be obtained in Chow and Liu [1].

Two-stage design: Alternatively, a two-stage crossover design described in Table 1 can be used to address interchangeability of switching. Under the two-stage design, qualified subjects are randomly assigned to receive either the test product or the reference product at the first stage. At the second stage, after a sufficient length of washout, subjects are randomly assigned to receive either the test product or the reference product with either equal or unequal ratio of treatment allocation. At the end of the study, the two-stage design will lead to four sequences of treatments, i.e., T T, T R, RT, and RR similar to those in Balaam's design.

Note that the above mentioned two-stage design that composes of a parallel phase (stage 1) and a crossover phase (stage 2) is similar to a placebo-challenging design proposed by Chow et al. [8]. As a result, statistical methods proposed by Chow et al. [8] are useful for data analysis from a two-stage design. Similarly, under the two-stage design the above comparisons (1)-(6) can also be made based on these methods.

Designs for alternation

To illustrate the conception of alternation, for example, for the alternating of "R to T to R" an appropriate study design should be used to assess the differences between "R to T" and "T to R", so as to determine whether the drug effect has returned to the baseline after the second switch. For this purpose, the following study designs are useful.

Two-sequence dual design: Two-sequence dual design is a 2×3 higher-order crossover design consisting of two dual sequences, namely T RT and RT R. Under the two-sequence dual design, the qualified subjects are assigned to the sequence of T RT or the sequence of RT R randomly. Of course, there is a sufficiently long washout time between dosing periods. By the two-sequence dual design, we will be able to evaluate the relative risk of alternating between the reference product and the test product, and the risk of using the reference product without any alternating.

Note that for analysis of data collected from a two-sequence dual design, the statistical methods, including the evaluation of average biosimilarity, the estimates of intra-subject variabilities and inference on carry-over effect, are given in Chow and Liu [1], at the same time they have discussed the expected values of the sequence-by-period means, analysis of variance table. In the case of missing data (i.e., incomplete data), statistical methods involved by Chow and Shao [9] are useful.

Williams design: For a broader sense of alternation, it is involving more than two biologics, e.g., two biosimilars T1 and T2 and one innovative product R, there are six possible sequences: (R, T2, T1), (T1, R, T2), (T2, T1, R), (T1, T2, R), (T2, R, T1), and (R, T1, T2). In this

	Designs							
Sequence	Switching			Alternating		Switching\ Alternating		
	Two Stage	Balaam's	Two Sequence Dual	Williams	Modified	Balaam's	Complete	Alternative
	1st	2nd						
1	T	RT	TT	TRT	RT_2T_1	TT	TTT	TTT
2	R	RT	RR	RTR	T_1RT_2	RR	RRR	RRR
3			TR		T_2T_1R	TRT	TRT	TRR
4			RT		T_1T_2R	RTR	RTR	RTR
5					T_2RT_1			
6					RT_1T_2			

Table 1: The list of these designs for switching, alternating, switching/alternating.

case, a 6×3 Williams design for comparing three products is useful (see, also, Chow et al. [1]). A Williams design is a variance-balanced design, which consists of six sequences and three periods. Under the 6×3 Williams design, the subjects who qualify the criterion, are assigned to one of the six sequences randomly. Within each sequence, there is a sufficiently long wash time between dosing periods (Table 1).

Detailed information regarding (1) construction of a Williams design, (2) analysis of variance table, and (3) statistical methods for analysis of data collected from a 6×3 Williams design adjusted for carry-over effects, in absence of unequal carry-over effects, and adjusted for drug effect can be given in Chow et al. [1].

Designs for switching/alternation

In the previous two sub-sections, useful study designs for addressing switching and alternating of drug interchangeability are discussed, respectively. Actually it is worth seeking to a study design which can address both switching and alternating. In this case, an intuitive study design is to combine a switching design with an alternating design. Along this line, in the following section, to address drug interchangeability clearer, several useful designs connecting both switching and alternating of drug interchangeability are introduced.

Modified balaam's design: As indicated earlier, Balaam's design is useful for addressing switching, while a two-sequence dual design is appropriate for addressing alternating. In the interest of addressing both switching and alternating in a single trial, we may combine the two study designs as follows: (T T, RR, T RT, and RT R), which consists of a parallel design (the first two sequences) and a two-sequence dual design (the last two sequences). This design will be called as modified Balaam's design, which is illustrated in Table 1.

As it can be seen from Table 1, data collected from the first two dosing periods, which are identical to the Balaam's design, can be used to address switching, while data from the last two sequences, can be used to assess the relative risks of alternating.

Complete design: As it can be shown that the modified Balaam's design is not a balanced design in terms of the number of dosing periods. If the balance in dosing periods is pursued, modified Balaam's design can be further modified as (T TT, RRR, T RT, RT R), we will refer to it as a complete design. The difference between the complete design and the modified Balaam's design is that the treatments are repeated at the third dosing period for sequences #1 and #2. A more accurate and reliable evaluation of intra-subject variability will be provided by the data collected from sequence #1, while data collected from sequence #2 is useful in establishing baseline for the reference product.

Note that statistical methods for analysis of data collected from the complete design are similar to those under the modified Balaam's design.

Alternative designs: For assessment of individual bioequivalence under a replicated design, Chow et al. [10] indicated that the optimal design among 2×3 crossover designs is so-called extra-reference design, which is given by (T RR, RT R). Thus, an alternative design is to combine a parallel design (T TT, RRR) and a 2×3 extra-reference design for addressing both switching and alternating. The resultant study design is then denoted by (T TT, RRR, RT R, T RR). Some advantages of the extra-reference design was given in Chow et al. [10], the test under the 2×3 extra-reference design are more powerful than the tests under the 2×3 crossover design. In fact in some cases the tests under the 2×3 extra-reference design are even comparable to the tests under the 2×4 design.

Adaptive designs: Currently, adaptive design methods in clinical research has attracted more and more notice because of the flexibility and efficiency in clinical trials Chow and Chang [11]. Similar ideas can be applied to assess biosimilarity and interchangeability of biosimilar products. For example, a two-stage adaptive design that combines two independent studies into a single trial may be useful. Some adaptations (modifications or changes) can be implemented after the review of accumulated data from the first stage. More detail discussions regarding various adaptive trial designs can be referenced in Chow and Chang [11].

Remarks

In Table 1, we give a list of these designs above mentioned. The Balaam's design and Two- stage design are used for the assessment of switching, by the two designs the risk of switching or no switching can be compared, and we can get a series comparisons such as the entries (1)-(6) in the section of Designs for Interchangeability. The difference between them is that the two-stage design includes a crossover design in stage 2; the intra-subject variability can be got in detail. The Two-sequence dual design and the Williams design serve for the assessment of alternating, they evaluate the continuous switch, such as "R to T to R", "T to R to T", but Williams design concerns on the broader sense such as "R to T1 to T2", the switch happens among more than one generic product. The modified Balaam's design, the complete design and the alternative design can assess the switching and alternating at the same time, they combine the parallel design and the cross-over design, the variability of inter-subject and the intra-subject can be estimated by the designs.

There is a clear distinction between the concepts for drug interchangeability for generic drugs and for biosimilar products. For drug interchangeability of generic drugs, the FDA suggests focusing on the assessment of the variability due to subject-by-product interaction, although its clinical relevance has not yet been fully understood and demonstrated. Alternatively, assessment of drug interchangeability of small molecule generics, due to subject-by-product adjusted for the intra-subject variability of the reference product, the assessment of the variability should be conducted. This new criterion is currently being studied by Endrenyi et al. [12].

Statistical Methods

In practice, switching and alternating can be assessed only after the biosimilar products under study have been proved to be highly similar to the innovative biological drug product. Connecting the idea of the development the biosimilarity index [1] to the proposed study design as described in the section of Designs for Interchangeability, a switching index and/or alternating index for addressing switching and/or alternating can be obtained, we can address the interchangeability of the biosimilars from two facets such as switching and alternation in this section.

Totality biosimilarity index

For a given criterion for biosimilarity and a valid study design, the biosimilarity index in a given functional area or domain will be given by the following steps [7]:

Step 1: Assess the 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 p is larger than a pre-specified number p0, where p0 can be obtained based on an estimate of reproducibility probability for a study of comparing a reference product to itself (the reference product), i.e., an R–R study.

Similar to what was described in Chow et al. [7], a totality biosimilarity index can be derived across all functional areas or domains by the following steps:

Step 1: Obtain, the biosimilarity index $\hat{p}_i$ for the *i* th domain;

Step 2: Define the totality biosimilarity index as $\hat{p}_T = \sum_{i=1}^{K} w_i \hat{p}_i$

where w_i is the weight for the *i* th domain, where $i = 1, 2....k$ (the number of domains or functional areas);

Step 3: Claim biosimilarity if the 95% confidence lower bound of p_T is greater than a pre-specified value p_{T0}, which can be determined based on an estimation of totality biosimilarity index for studies comparing a reference product to itself (the reference product).

As mentioned above, the totality biosimilarity index can be found some merits that (1) regardless of study design employed, the selection of the study end point and the diversity of biosimilar criterion, the development of biosimilarity index is robust, (2) the variability is taken into consideration, which is the major criticisms in the evaluation of average bioequivalence, (3) the degree of similarity is defined and assessed, that is, it can answer partially the generally question that "how similar is considered similar?", and (4) at last the sensitivity of heterogeneity in variance will been reflected by the use of biosimilarity index or totality biosimilarity index.

Switching index (SI)

Similarly a switching index can be developed by the aid of an appropriate study design such as a 4×2 Balaam crossover design mentioned former. Thus, for addressing the issue of switching, biosimilarity for "R to T", "T to R", "T to T", and "R to R" needs to be assessed.

Define $\hat{p}_{Ti}$ the biosimilarity index for the ith 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). Like described in Chow et al. [7], the switching index (SI) can be obtained as follows:

Step 1: Obtain $\hat{p}_{Ti}$, *i*=1,...,4;

Step 2: Define the switching index as SI= $\max_i \{\hat{p}_{Ti}\}$, *i*=1,...,4, which is the largest order of the biosimilarity indices;

Step 3: Claim switchability if the 95% confidence lower boundof SI is larger than a pre-specified value p_{s0}.

As a result, the 95% confidence low bound of SI can be obtained. Then we claim switching if the 95% confidence low bound for SI is greater than p_{s0}.

Alternating index (AI)

According to the conception of biosimilarity index in Chow et al. [7], the alternating index can be obtained under the modified Balaam's crossover design of (T T, RR, T RT, RT R), biosimilarity for "R to T to R" and "T to R to T " needs to be assessed for the evaluation of alternating. Define p_{Ti} as the totality biosimilarity index for the ith switch, where *i*=1 (switch from R to R), 2 (switch from T to T), 3 (switch from R to T), or 4 (switch from T to R). As a result, the alternating index (AI) can be obtained [1] as follows:

Step 1: Obtain $\hat{p}_{Ti}$, *i*=1, ...,4;

Step 2: Define the range of these indexes, AI= $\{\hat{p}_{Ti}\} - \min_i \{\hat{p}_{Ti}\}$, *i*=1,...,4 as the alternating index;

Step 3: Claim alternation if the 95% confidence lower bound of AI is larger than a pre- specified value P_A.

Thus, we can get the estimate of the alternative index AI, if the 95% confidence lower bound for AI is greater than PA, the conclusion of alternation can be obtained. Therefore, interchangeability is claimed if both switching and alternation are concluded.

Remarks

Under the appropriate study designs, we propose the switching index and alternating index to assess the switching and alternating, it is same to biosimilarity index (totality biosimilarity index) for assessment of biosimilarity. These assessments is based on the reproducibility probability, obviously they are the probability indices, in fact, it also can be considered in moment-based as follows

$$\hat{z}_d = \frac{\hat{\mu}_T - \hat{\mu}_R}{\hat{\sigma}_d}$$

where $\hat{z}_d$ is a standardized score for measuring the distance between the generic/test (T) and the innovative/reference (R) products. In this case, the biosimilarity index can be defined as BI= $\hat{z}_d$ or BI= $\Phi(\hat{z}_d)$, where Φ is a standard normal distribution function.

Concluding Remarks

The concept of drug interchangeability in terms of prescribability and switchability for small molecule drug products is similar but different from that for large molecule biological products. Thus, the usual methods for addressing drug interchangeability through the assessment of population/individual bioequivalence cannot be used for the assessment of drug interchangeability for biosimilar products directly.

Based on the totality biosimilarity index, the switching index and alternating index to address drug interchangeability of biosimilars can be obtained under an appropriate switching design and alternating design, respectively. The proposed switching/alternating indices have some advantages that (1) they can be used in any criteria for biosimilarity and study designs, (2) based on the relative difference the assessment is conducted with the reference product, (3) they can answer partially the questions that "how similar is considered highly similar?", "the degree of similarity", and "interchangeability from the two facets: switching and alternating", (4) The given approach is consistent with the current regulatory rules.

However, it should be noted that the selection of weight in each domain is worth discussing and complicated, which affects the estimate of totality biosimilarity index and/or switching/alternating indices largely.

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