where $k_1 = 1$ and $k_2 = 4$ denote the orders of the difference. On the other hand, the upper bound for the variance of AI could be obtained by

$$\begin{aligned}\mathrm{Var}(\mathrm{AI}) &= \mathrm{Var}\left(P_{T_{(1)}}\right) + \mathrm{Var}\left(P_{T_{(4)}}\right) + 2\mathrm{Cov}\left(P_{T_{(1)}}, P_{T_{(4)}}\right) \\ &< \mathrm{Var}\left(P_{T_{(1)}}\right) + \mathrm{Var}\left(P_{T_{(4)}}\right) + 2\mathrm{Var}\left(P_{T_{(1)}}\right)^{1/2} \mathrm{Var}\left(P_{T_{(4)}}\right)^{1/2} \\ &< n\sigma^2 + n\sigma^2 + 2n\sigma^2 = 16\sigma^2,\end{aligned}$$

which is derived based on the Cauchy-Schwarz inequality (Casella and Berger, 2002) and the result for the upper bound of the variance of order statistics (Papadatos, 1997). 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 larger than p_{A_0}. Therefore, we may claim interchangeability if both switching and alternating are concluded.

11.4.4 Remarks

The above biosimilarity index (totality biosimilarity index) for the assessment of biosimilarity and the switching index and/or alternating index for the assessment of interchangeability are developed based on the reproducibility probability. Hence, they are probability-based indices. In practice, we may consider moment-based indices for the assessment of biosimilarity and interchangeability. For example, we may consider

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

a standardized score for measuring the distance between the test (T) and reference (R) products. In this case, the biosimilarity index can be defined as $\mathrm{BI} = \hat{z}_d$ or $\mathrm{BI} = \Phi(\hat{z}_d)$.

11.5 CONCLUDING REMARKS

With small-molecule drug products, bioequivalence generally reflects therapeutic equivalence. Drug prescribability, switching, and alternating are generally considered reasonable. With biological products, however, variations are often higher (other than pharmacokinetic factors may be sensitive to small changes in conditions). Thus, often only parallel-group design rather than crossover kinetic studies can be performed. It should be noted that with follow-on biologics, biosimilarity does *not* reflect therapeutic comparability. Therefore, switching and alternating should be pursued with extreme caution.

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 as defined in the BPCI Act. Thus, the usual methods for addressing drug interchangeability through the assessment of population/