a drug product (e.g., a brand-name drug product) to an alternative drug product (i.e., a biosimilar of the brand-name drug product) within the same subject, whose concentration of the drug product has been titrated to a steady, efficacious, and safe level. As a result, drug switchability is considered more critical than drug prescribability in the study of drug interchangeability for patients who have been on medication for a while. Drug switchability, therefore, is exchangeability within the same subject.

Issues of interchangeability, switchability, and substitution of biosimilars are discussed in Chapter 10 of this book.

1.3.8 Development of the Biosimilarity Index

Chow (2011) proposed the development of a composite index for assessing biosimilarity based on the facts that (1) the concept of biosimilarity for biological products (made of living cells) is very different from that of bioequivalence for chemical drug products and (2) critical quality attributes of biological products are dependent on the manufacturing process. Although some research on the comparison of moment-based criteria and probability-based criteria for the assessment of (1) average biosimilarity and (2) variability of biosimilarity for some given study endpoints by applying the criteria for bioequivalence are available in the literature (see, e.g., Chow and Liu, 2010; Hsieh et al., 2010), universally acceptable criteria for biosimilarity are not available in the regulatory guidelines/guidances. Thus, Chow (2011) proposed a biosimilarity index based on the concept of the probability of reproducibility as follows:

Step 1: Assess the average biosimilarity based on bioequivalence criteria—that is, biosimilarity is claimed if the 90% confidence interval of the ratio of means of a given study endpoint falls within the biosimilarity limit of (80%, 125%) based on log-transformed data.

Step 2: Once the product passes the test for biosimilarity in Step 1, calculate the probability of reproducibility (Shao and Chow, 2002) based on the observed ratio and variability. The primary reason for this is to take the variability and the sensitivity of heterogeneity in variances into consideration.

Step 3: We shall claim biosimilarity if the probability of reproducibility is larger than a prespecified number p_0, which can be obtained based on the comparison of a "reference product" to the "reference product." For example, if the R-R comparison suggests a reproducibility of 60%, then p_0 could be chosen as 80% of the 60%, which is 48%.

As indicated by Chow (2011), the above proposal has the advantages that (1) we still follow the well-established criterion for the assessment of bioequivalence, which has been used for decades and (2) the probability of reproducibility will reflect the sensitivity of heterogeneity in variance. Note that the proposed biosimilarity index is developed based on the probability of reproducibility. It can be applied to different functional areas (domains) of biological products such as PK, biological activities, biomarkers (e.g., pharmacodynamics), immunogenicity, the