Therefore, for the moment-based measures, if the test formulation is indeed bioequivalent to the reference formulation, then $d(Y_T;Y_R)$ should be very close to $d\left(Y_R;Y_R'\right)$. It follows that if the criteria are functions of the difference (or ratio) between $d(Y_T;Y_R)$ and $d\left(Y_R;Y_R'\right)$, bioequivalence is concluded if they are smaller than some prespecified limit. For probability-based measures, however, if the test formulation is indeed bioequivalent to the reference formulation, as compared with $d\left(Y_R;Y_R'\right)$, $d(Y_T;Y_R)$ should be relatively large. As a result, bioequivalence, or biosimilarity, is concluded if the criterion based on the probability-based measure is higher than some prespecified limit (Chow et al., 2010).

1.3.1.4 Remarks

Although several criteria for similarity are available in both regulatory guidelines/guidances and the literature, these criteria do not translate each other. In other words, one may pass one criterion but fail to pass others. Moreover, these criteria do not address the following critical questions: (1) how similar is considered to be similar? and (2) what is the impact of the level of similarity on drug interchangeability.

1.3.2 Statistical Methods

Since there are many critical attributes of a potential patient's response in follow-on biologics, for a given critical attribute, valid statistical methods need to be developed under a valid study design and a given set of criteria for similarity, as described in Section 1.3.1. Several areas can be identified for developing appropriate statistical methodologies for assessment of the biosimilarity of follow-on biologics. These areas include, but are not limited to:

1. Consistency in manufacturing processes
   Since changes in the manufacturing process could have a significant impact on the clinical outcome of follow-on biologics, tests for consistency in manufacturing processes are critical in the assessment of biosimilarity.
2. Stability testing (multiple labs, multiple lots)
   Since biological products are sensitive to environmental factors such as light and temperature, we suggest that stability testing be conducted under study designs that can account for these environmental factors following both the International Conference on Harmonization (ICH) and FDA guidelines for determination of shelf life.
3. Comparability in quality attributes of structural and functional characterization
   As indicated by the FDA, test for comparability in quality attributes in structural and functional characterization is essential for assessment of the biosimilarity of follow-on biologics. Valid statistical methods are necessarily developed with respect to the study design, endpoints, and criteria employed.
4. Sequential testing procedures
   Due to the complexity of the manufacturing process of biological products, sequential testing procedures for statistical quality control may be useful to ensure biosimilarity.