5. Criteria for biosimilarity (in terms of average, variability, or distribution) to address the question of "how similar is similar"
   We suggest establishing criteria for biosimilarity in terms of average, variability, and/or distribution.
6. Criteria for interchangeability
   In practice, it is recognized that drug interchangeability is related to the variability due to subject-by-drug interaction. However, it is not clear whether a criterion for interchangeability should be based on the variability due to subject-by-drug interaction or on the variability due to subject-by-drug interaction adjusted for intrasubject variability of the reference drug.
7. Bridging studies for assessing biosimilarity
   Because most biosimilar studies are conducted using a parallel design rather than a replicated crossover design, independent estimates of variance components such as the intrasubject and the variability due to subject-by-drug interaction are not possible. In this case, bridging studies may be considered.
8. Use of a percentile method for the assessment of variability
   In addition to classical F-type test statistics for assessment of variability, use of a percentile method may be useful.
9. Assessment of immunogenicity
   As indicated by the FDA, assessment of immunogenicity is important for assessment of biosimilarity. Appropriate statistical methods should be developed according to study endpoints and criteria employed.
10. Multiple testing procedures for global assessment of biosimilarity
    Since the assessment of biosimilarity of follow-on biologics comprises different properties such as biological activities, PK/PD, immunogenicity, and clinical response, multiple testing procedures should be considered for the assessment of global biosimilarity.

In addition to PK/PD, biomarkers such as genomic data could serve as surrogate endpoints for the assessment of biosimilarity of follow-on biologics if they are predictive of clinical responses.

1.3.3 The Manufacturing Process

Unlike small-molecule drug products, biological products are made of living cells. Thus, the manufacturing of biological products is a very complicated process that involves (1) cell expansion, (2) cell production (in bioreactors), (3) recovery (through filtration or centrifugation), (4) purification (through chromatography), and (5) formulation. A small discrepancy at each step (e.g., purification) could lead to a significant difference in the final product, which might cause a difference in clinical outcomes. Thus, process control and validation plays an important role in the success of the manufacturing of biological products. In addition, since at each step (e.g., purification), different methods may be used for different biological manufacturing processes (within the same company or at different biotech companies), tests for consistency are