3.1 BACKGROUND

Following passage of the Biologics Price Competition and Innovation (BPCI) Act in 2009, the FDA circulated three guidances on the demonstration of biosimilarity of biosimilar products for public comments in April 2015 (FDA, 2015a,b,c). These guidances are intended not only (1) to assist sponsors to demonstrate that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting a marketing application under Section 351(k) of the Public Health Service (PHS) Act, but also (2) to describe the FDA's current thinking on factors demonstrating that a proposed protein product is highly similar to a reference product, which was licensed under Section 351(a) of the PHS Act. In the guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, the FDA introduces the concept of a stepwise approach to obtaining "Totality of the Evidence" for the regulatory review and approval of biosimilar applications (FDA, 2015a).

The stepwise approach starts with the assessment of analytical similarity of critical quality attributes (CQAs) for structural and functional characterization in the manufacturing process of biosimilar products that may have an impact on the assessment of similarity. In practice, often a large number of CQAs may be relevant to clinical outcomes. Thus, it is almost impossible to assess analytical similarity for all of these CQAs individually. As a result, the FDA suggests that the sponsors identify CQAs that are relevant to clinical outcomes and classify them into three tiers depending on their criticality risk ranking—most relevant (Tier 1), mild to moderately relevant (Tier 2), and least relevant (Tier 3) to clinical outcomes. To assist the sponsors, the FDA also proposes some statistical approaches for the assessment of analytical similarity for CQAs from different tiers. For example, the FDA recommends an equivalence test for CQAs from Tier 1, a quality range approach for CQAs from Tier 2, and descriptive raw data and graphical presentation for CQAs from Tier 3 (see, e.g., Chow, 2013, 2014, 2015; Christl, 2015; Tsong, 2015).

This chapter not only provides a close look at these approaches by providing interpretation and/or statistical justification whenever possible, but also discusses some challenging issues to the FDA's proposed approach (mainly on the equivalence test for Tier 1 CQAs). In addition, some recommendations and alternative methods are proposed.

In the next section, the stepwise approach for demonstrating biosimilarity as suggested by the FDA draft guidance is briefly outlined. Assessment of quality attributes is given in Section 3.3. Section 3.4 provides brief descriptions of the equivalence test, the quality range approach, and the method of descriptive raw data and graphical comparison. Some challenging issues to the FDA's proposed approaches are discussed in Section 3.5. Section 3.6 provides recommendations and alternative methods for the assessment of analytical similarity in CQAs from different tiers. Some concluding remarks are given in the last section of this chapter.

3.2 STEPWISE APPROACH FOR DEMONSTRATING BIOSIMILARITY

As defined in the BPCI Act, a biosimilar product is a product that is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences in terms of safety, purity,