7.1 TOTALITY OF EVIDENCE

As documented in other chapters, the development of biosimilars in "highly regulated" regions of the world [i.e., those countries that subscribe to the standards of the International Committee for Harmonization (ICH)—including Europe, the US, and Japan, as the formal members of ICH, and also Canada and Australia] follows a "totality of the evidence" model, with the development proceeding in a "stepwise" fashion. The overall focus of the biosimilar development program is to prove that the biosimilar contains "essentially the same biological substance" as the reference product (EMA, 2012). It is important for the practicing physician to have confidence when using a biosimilar that it is just like changing the batch of the reference product, and this is indeed the case considering the natural variation existing in all biological products (Schiestl et al., 2011). Consequently, the clinical trials in support of regulatory approval of a biosimilar are designed to "confirm similarity" established analytically and not to demonstrate the safety and efficacy of the biosimilar in all indications for which the reference product is already approved. Because of this unique role of clinical trials to confirm similarity, there are many design features, outlined below, that fundamentally differ from traditional drug development clinical trials used for initial approval of a novel biological drug or for the addition of an indication.

Before discussing the design characteristics of biosimilar clinical trials, it will be helpful to understand how the approach to clinical development of biosimilars has evolved beyond the studies applied in traditional regulatory science for originator products. This evolution began with the introduction of recombinant biological products in the 1980s. Adoption of these new drugs into clinical practice required sponsors to make more material than could be originally anticipated, and this scale-up plus the rapid developments in biotechnology belied the old "product is the process" approach to biologics. The production of chemically synthesized small-molecule drugs involves the creation of the identical active pharmaceutical ingredient with every batch. However, manufacturing recombinant biological drugs does not usually produce a single identical biological product. Just like in living organisms, the host cells involved in synthesizing the biological drug, coded by the recombinant DNA program, modify the protein after synthesis of the basic amino acid and protein structure. This is called posttranslational modification. These modifications, such as glycosylation or terminal amino acid modification, produce a mixture of biological product in an equilibrium within the recombinant cell system. The final product, purified from these cells, is nonetheless designed to have the same clinical effect over multiple batches.

The pharmaceutical sponsors must provide evidence that they have good control of their manufacturing process so that batch-to-batch variability is within specific acceptance criteria. This applies to all biologics irrespective of whether they are recombinant or naturally sourced, but recombinant technology has provided new opportunities for scale-up and control. Increasing acceptance and expanded use of recombinant biologics led to the need to manufacture more drugs than the maximal capacity of the original manufacturing process. To expand the manufacturing capacity, the sponsors had to "scale-up" the manufacturing process or transfer the manufacturing process to a larger facility. As pointed out by Schiestl et al., such a scale-up or transfer induces a "manufacturing change" that can be measurable