characterization of critical quality attributes (CQAs) that are relevant to clinical outcomes at various stages of the manufacturing process; animal studies for toxicity; pharmacokinetics and pharmacodynamics for pharmacological activities; clinical studies for efficacy confirmation; immunogenicity for safety and tolerability; and pharmacovigilance for long-term safety. Accordingly, the purpose of this chapter is to outline scientific factors and practical issues that are commonly encountered in the development of biosimilar products.

Section 1.2 describes fundamental differences and assumptions between conventional drug products and follow-on biologics. Section 1.3 presents scientific factors and practical issues that are commonly encountered in the development of biosimilar products. The aim and scope of the book are provided in Section 1.4.

1.2 FUNDAMENTAL DIFFERENCES FROM GENERICS AND ASSUMPTIONS FOR BIOSIMILARS

1.2.1 Fundamental Differences from Generics

In comparison with conventional drug products, the concept for the development of follow-on biologics is very different. Webber (2007) defines follow-on (protein) biologics as products that are intended to be sufficiently similar to an approved product to permit the applicant to rely on existing scientific knowledge about the safety and efficacy of the approved reference product. Under this definition, follow-on products are intended not only to be similar to the reference product, but also to be therapeutically equivalent with the reference product. As a number of biological products patents have expired and many more are due to expire in the next few years, the subsequent follow-on products have generated considerable interest within the pharmaceutical/biotechnological industry as biosimilar manufacturers strive to obtain part of an already large and rapidly growing market. The potential opportunity for price reductions versus the innovator biologic products remains to be determined, as the advantage of a cheaper price may be outweighed by the potential increased risk of side-effects from biosimilar molecules that are not exact copies of their innovators. In this chapter, we focus on issues surrounding biosimilars, including manufacturing, quality control, clinical efficacy, side-effects (safety), and immunogenicity. In addition, we attempt to address the challenges in imposing regulations that deal with these issues.

1.2.2 Fundamental Assumptions

As indicated by Chow and Liu (2008), bioequivalence studies are performed under the so-called Fundamental Bioequivalence Assumption, which constitutes the legal basis for the regulatory approval of generic drug products. As noted earlier, the Fundamental Bioequivalence Assumption states:

> If two drug products are shown to be bioequivalent, it is assumed that they will reach the same therapeutic effect or they are therapeutically equivalent and hence can be used interchangeably.