1.1 BACKGROUND

When an innovative drug product is going off patent, generic companies may file an abbreviated new drug application (ANDA) for the approval of the generic copies (with an identical active ingredient) of the innovative drug product under the Hatch–Waxman Act. For approval of generic drug products, the United States Food and Drug Administration (FDA) as well as other regulatory agencies require that evidence in average bioavailability be provided through the conduct of pharmacokinetic (PK) bioequivalence (in terms of rate and extent of drug absorption) studies. The assessment of bioequivalence as a surrogate endpoint for the evaluation of drug safety and efficacy is based on the *Fundamental Bioequivalence Assumption*. It states that if two drug products are shown to be bioequivalent in average bioavailability, it is assumed that they are therapeutically equivalent and can be used interchangeably.

Unlike drug products with identical active ingredients, the concept for the development of copies of biological products is different because they are made of living cells. The copies of biological products are referred to as biosimilars by the European Medicines Agency (EMA), similar biotherapeutic products (SBPs) by the World Health Organization (WHO), and subsequent-entry biologics (SEB) by Health Canada.

Biosimilars are fundamentally different from generic (chemical) drugs. Important differences include the size and complexity of the active substance and the nature of the manufacturing process. Because biosimilars are not exact copies of their originator products, different criteria for regulatory approval are required. This is partly a reflection of the complexities of manufacturing and the safety and efficacy controls of biosimilars when compared to their small-molecule generic counterparts (see, e.g., Chirino and Mire-Sluis, 2004; Crommelin et al., 2005; Roger and Mikhail, 2007; Schellekens, 2005). Since biological products are (recombinant) proteins produced by living cells, manufacturing processes for biological products are highly complex and require hundreds of specific isolation and purification steps. In practice, it is impossible to produce an identical copy of a biological product, as changes to the structure of the molecule can occur with changes in the production process. Since a protein can be modified during the process (e.g., different sugar chains may be added, the structure may have changed due to protein misfolding and so on), different manufacturing processes may lead to structural differences in the final product, which may result in differences in efficacy and safety, and may have an impact on the immune responses of patients. In some cases, these issues also occur during the postapproval changes of the innovator's biological products.

Since 2006, the EMA has provided several guidelines for the development of biosimilars. These have been followed by guidelines established by other regulatory agencies (Australia, Japan, South Korea, Canada) and the WHO. In 2015, the FDA published several guidances on the development of biosimilar products (FDA, 2015a–c). The guidance entitled *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* recommends a stepwise approach for obtaining the totality of the evidence for assessing biosimilarity between a proposed biosimilar product and its corresponding innovative biological drug product. The stepwise approach starts with analytical similarity assessment for functional and structural