8.3 CRITERIA FOR BIOSIMILARITY

As indicated in Chow and Liu (2008), bioequivalence assessment for generic drug products is possible under the Fundamental Bioequivalence Assumption. It states that if two drug products are shown to be bioequivalent in the drug absorption profile (which is measured in terms of the extent and rate of absorption), it is assumed that they will reach the same therapeutic effect or they are therapeutically equivalent. The Fundamental Bioequivalence Assumption assumes that there is an association between pharmacokinetic responses and clinical outcomes. This assumption, however, may not be applicable for the assessment of biosimilarity of biosimilars due to the fundamental differences between generic (small molecular) drug products and similar biological (large molecular) drug products (see Table 8.2).

In what follows, several criteria for the primary assessment of bioequivalence or similarity proposed by the FDA are discussed for their applicability to the assessment of biosimilarity.

8.3.1 Average Bioequivalence (Biosimilarity)

For the assessment of average bioequivalence (ABE) both *in vivo* and *in vitro*, the FDA adopted a one-size-fits-all criterion. That is, for *in vivo* (*in vitro*) bioequivalence assessment, a test drug product is said to be bioequivalent to a reference drug product if the estimated 90% confidence interval for the geometric means ratio (GMR) of the primary pharmacokinetic (PK) parameters (e.g., the area under the blood or plasma concentration-time curve (AUC)) and maximum concentration (C_{max}) is totally within the bioequivalence limits of 80.00%–125.00%. See, for example, Chow and Liu (2008), FDA (2003, 2013), and Chow (2011).

The one-size-fits-all criterion does not take into consideration the therapeutic window and intrasubject variability of a drug which has been identified to have non-negligible impact on the safety and efficacy of generic drug products, as compared to the innovative drug products. In the past several decades, this one-size-fits-all

TABLE 8.2
Fundamental Differences between Generic Drugs and Biosimilars

Generic Drugs	Biological Drugs (Biosimilars)
Made by chemical synthesis	Made by living cells
Defined structure	Heterogeneous structure
	Mixtures of related molecules
Easy to characterize	Difficult to characterize
Relatively stable	Variable
	Sensitive to environmental conditions such as light and temperature
No issue of immunogenicity	Issue of immunogenicity
Usually taken orally	Usually injected
Often prescribed by a general practitioner	Usually prescribed by specialists