can alter the benefit–risk profile of the drug. Changes in the manufacturing process may also result in alterations to the product that may or may not be clinically significant. Changes, such as differences in the primary amino acid sequence, may lead to significant heterogeneity. Likewise, modifications to amino acids, sugar moieties (due to glycosylation), or other side chains can affect the potency or degradation of the biotherapeutic, the antigenic sites, and the solubility of the protein. Generation of new antigenic epitopes in the protein may increase the antigenicity of the product. Also, changes in the tertiary folding of the protein may result in protein aggregation, oxidation, and deamidation, leading to an increased immunogenic response to the drug. Such changes may be introduced by several factors, including the manufacturing process and environmental conditions such as exposure to light, changes in temperature, moisture content, shear, or the material used for packaging. In addition, impurities introduced in the final product, due either to the manufacturing process or to the product itself, may increase the probability of a severe immune reaction to a protein product (De Groot and Scott, 2007; Zuniga and Calvo, 2010; Weise et al., 2012; Socinski et al., 2015).

13.2 SCIENTIFIC GUIDELINES FOR THE REGULATION OF BIOSIMILARS

Generic versions of chemically synthesized medicines follow well-established scientific standards that have been put in place by regulatory authorities worldwide. Authorization of a generic medicine is based on proving its chemical identity and its bioequivalence to the reference product. If the test product and reference product are comparable in dosage forms, contain identical amounts of the identical medicinal ingredient(s), and display similar pharmacokinetic profiles, they are said to be bioequivalent. Generic medicines are usually authorized on the basis of abbreviated applications. Nonclinical and clinical studies that are required for reference drug products are usually not required for generic products. However, regulators are aware that the prototype bioequivalence guidance that has worked well for generic products is not applicable to complex, biologically derived drugs. Therefore, specific guidelines have been developed by various international regulatory authorities to deal with the challenges related to the authorization and pharmacovigilance of biosimilars.

In principle, the guidance document on technical requirements for registration of pharmaceuticals for human use developed by the International Council of Harmonization (ICH) is applicable for biosimilar products as well. The WHO released guidelines on the evaluation of similar biotherapeutic products (SBPs) in 2009. These guidelines are intended for regulatory agencies to provide guidance for the evaluation, authorization, and regulation of biosimilars (WHO, 2009).

The European Union (EU) was the first to develop such a guidance document as an annex to Directive 2001/83/EC. It details a new process for the authorization of biological medicines. In this guidance, the agency added the requirement for safety and efficacy data, in addition to the studies to demonstrate the similarity between reference and biosimilar product. In the EU, the general principles for regulation of