Briefly, the basic principle of a biosimilar development program is to establish the similarity between the biosimilar and the reference product using the best possible strategy, ensuring that previously demonstrated safety and efficacy for the reference product are also applicable to the biosimilar. The biosimilar must be equivalent to the reference medicine in physicochemical and biological characteristics, and any observed differences will have to be duly justified in relation to their potential impact on safety and efficacy. Any differences that may result in an advantage in terms of safety (e.g., lowest levels of impurities or less immunogenicity) should be explained but are not incompatible with the establishment of biosimilarity.

A step-by-step approach is recommended for the development of a biosimilar, that is, starting with a complete and detailed physicochemical and biological characterization. The scope and amount of the nonclinical and clinical studies will depend on the level of evidence obtained in the previous step, including the robustness of the physicochemical, biological, and nonclinical *in vitro* data and the extent of any structural differences identified between the biosimilar and the reference product.

The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference product that could have an impact on efficacy and/or safety. Therefore, the clinical studies must be sufficiently sensitive in design, population, endpoints, and implementation to detect such differences if they were present.

Once the marketing authorization is granted, there is no regulatory requirement for redemonstration of comparability because it is acknowledged that the biosimilar will have its own life cycle (in the same way as the reference product has its own). Demonstration of biosimilarity is just a special marketing authorization procedure. Once commercialized, the biosimilar is an alternative product on the market in the relevant therapeutic area, and its production process and control are subject to optimization and evolution, as it is the case with innovative medicines or the reference medicinal product. After changes in the manufacturing process and for demonstration of comparability, the same rules apply for both originators and biosimilars (see also the following section).

15.3.2 Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues

This guideline came into force on June 1, 2006, and has been reviewed recently (EMA, 2012). It describes the requirements for the manufacturing process and control of the biosimilar medicinal product, quality comparability studies, taking into account the choice of the reference medicine, analytical, physicochemical characterization, biological activity, purity, and quality attributes to establish the relevant specifications of the biosimilar. Although the guide refers to biotech drugs, the principles described could be applied to other biological products.

Biosimilar medicines are manufactured and controlled according to their own development and in accordance with relevant guidelines (ICH and CHMP; see the EMA website). The content of Module 3 (production and control data) of the