choice of single-dose studies, steady-state studies, or repeated determination of PK parameters, and the study population. Owing to the lack of established acceptance criteria for the demonstration of similar PK between SBP and RBP, the traditional 80%–125% equivalence range is often used. Besides, PD studies and confirmatory PK/PD studies may be appropriate if there are clinically relevant PD markers. In addition, the similar efficacy of SBP and RBP has to be demonstrated in randomized and well-controlled clinical trials, which should preferably be double-blind or at least observer-blind. In principle, equivalence designs (requiring lower and upper comparability margins) are clearly preferred for the comparison of the efficacy and safety of SBP with RBP. Noninferiority designs (requiring only one margin) may be considered if appropriately justified. The WHO also suggests that prelicensing safety and immunogenicity data should be obtained from the comparative efficacy trials.

In addition to the nonclinical and clinical data, applicants also need to present an ongoing risk management and pharmacovigilance plan, since data from preauthorized clinical studies are usually too limited to identify all potential side effects of the SBP. The safety specification should describe important identified or potential safety issues for the RBP and any that are specific for the SBP.

In summary, the WHO guidelines on evaluating similar biotherapeutic products represent an important step forward in the global harmonization of biosimilar product evaluation and regulation, and provide clear guidance for both regulatory bodies and the pharmaceutical industry.

8.2.2 The European Union

The EU has pioneered the development of a regulatory system for biosimilar products. The EMA began formal consideration of scientific issues presented by biosimilar products at least as early as January 2001 when an *ad hoc* working group discussed the comparability of medicinal products containing biotechnology-derived proteins as active substances (CPMP, 2001). In 2003, the European Commission amended the provisions of the EU's secondary legislation governing requirements for marketing authorization of applications for medicinal products to establish a new category of applications for "similar biological medicinal products" (CD, 2003). In 2005, the EMA issued a general guideline to introduce the concept of similar biological medicinal products, to outline the basic principles to be applied, and to provide applicants with a "user guide" showing where to find relevant scientific information (EMA, 2005). Since then, 14 biosimilar products have been approved by EMA under the pathway. One of the rejected biosimilars is Alpheon (interferon α-2a). It was developed by BioPartners GmbH and designed to become a biosimilar of the reference product Roferon-A for the treatment of adult patients with chronic hepatitis C. The EMA refused the marketing authorization for Alpheon due to the difference identified between Alpheon and the reference product, such as impurities, stability, and side effects.

8.2.2.1 Key Principles and Basic Concept

Unlike the WHO guideline which seems to focus more on recombinant DNA-derived therapeutic proteins, EMA's guidelines clearly indicate that the concept of a "similar biological medicinal product" is applicable to a broad spectrum of products