2006 lays down the nonclinical and clinical requirements for a biological medicinal product claiming to be similar to one already marketed (EMA, 2006e). The nonclinical section of the guideline addresses the pharmacotoxicological assessment, and the clinical section addresses the requirements for PK/PD and efficacy studies. Clinical safety studies as well as the risk management plan, with special emphasis on studying the immunogenicity of the biosimilar products, are also required. In 2011, EMA published a concept paper on the revision of this guideline (EMA, 2011c) that indicates several issues in need of discussion for a potential revision. First, EMA emphasizes the need to follow the 3Rs principles (replacement, reduction, and refinement) with regard to the use of animal experiments. Second, a revised version of the guideline will consider a risk-based approach for the design of an appropriate nonclinical study program. Third, the guideline should be clearer considering the need and acceptance of pharmacodynamics markers, and the measures that should be taken in the event relevant markers are not available. It should be noted, however, that the EMA issued a biosimilarity guideline in October, 2014, making an attempt to address these issues (EMA, 2014).

8.2.2.5 Product Class–Specific Guidelines

The principles of biosimilar drug development discussed earlier in this chapter apply in general to all biological drug products. However, there are no standard datasets that can be applied to the approval of all classes of biosimilars. Each class of biologic varies in its benefit/risk profile, the nature and frequency of adverse events, the breadth of clinical indications, and whether surrogate markers for efficacy are available and validated. Accordingly, the EMA has developed product class–specific guidelines that define the nature of comparative studies. So far, guidance for the development of biosimilar products has been developed for six different product classes: erythropoietins, insulins, growth hormones, alpha interferons, granulocyte-colony stimulating factors, and low-molecular-weight heparins (LMWHs), as well as beta interferons, follicle stimulation hormone, and monoclonal antibodies (EMA, 2006a,b,c,d, 2010a,b, 2011d).

8.2.2.6 European Experiences

As indicated earlier, the EMA has issued scientific guidelines on the quality, nonclinical, and clinical standards for the approval of biosimilars. The EMA has issued product class–specific guidelines (including EPO, G-CSF, insulin, growth hormone, LMW heparin, and interferon-α). According to these product class–specific guidelines, as of December 31, 2010, 14 biosimilar drugs have been approved in Europe. As compared to other regions in the world, Europe holds the highest number of biosimilar approvals. This number is expected to increase as many biologic patents will expire in the near future, which will help increase market size and competition among market participants.

8.2.2.7 Remarks

In summary, the EU has taken a thoughtful and evidence-based approach and has established a well-documented legal and regulatory pathway for the approval of biosimilar products distinct from the generic pathway. In order to grant a