The FDA has established labeling requirements for biosimilars including a designation as to whether the biosimilar is interchangeable with the reference product (FDA, 2015; GaBI Online, 2015f). However, decisions regarding automatic substitution are left up to the states. At least thirteen states in the US have passed legislation so far allowing substitution of biosimilars for reference products (GaBI Online, 2015g).

As more experience is gained with the use of biosimilars, more regulatory agencies are reconsidering their initial strict approach to interchangeability and substitution toward a more relaxed view. Once the biosimilar is on the market, it becomes an alternative within the same therapeutic group as the reference medicine and others that are equivalent and, therefore, it should be treated as such. When considering switching a patient from a particular biological medicinal product to a biosimilar, the same rules as applied for products within the same therapeutic class should be followed; that is, it is the responsibility of the treating physician and the patient, or it is done following specific local substitution policies or internal protocols at a particular hospital or health care center.

Interchangeability and substitution of biosimilars are discussed in detail in Chapter 10 of this book.

15.6 CONCLUDING REMARKS

In the EU, the regulatory framework for the development of biosimilar medicinal products is well established and provides relatively clear recommendations in terms of quality, nonclinical, and clinical criteria for their development. These recommendations are continuously kept under review as more experience is gained with their use; additional challenges are posed through scientific advice and in accordance with the evolution of scientific knowledge in specific therapeutic areas. More emphasis is given to a solid, robust, and state-of-the-art quality development, as it is the area where differences can be detected easily as characterization techniques are becoming more sensitive. *In vitro* functional studies using different techniques and cell-based systems allow a deeper evaluation of the significance of those differences, while *in vivo* nonclinical studies are being reduced as the information they provide is very limited and there is already wide clinical experience with the reference medicinal product. The requirements for clinical studies are also being refined as it is recognized that in some cases they would not have enough sensitivity to detect differences between two similar products. Extrapolation of indications probably remains the most controversial issue; therefore, regulators should still make an additional effort to better communicate their rationale for the decisions made as more biosimilars are approved. This will contribute to a better understanding of the regulatory requirements and decisions that will be useful for prescribing physicians and learned societies and will certainly support the use of biosimilars. Regulators recognize the limitations of the safety database (including immunogenicity data) at the time of marketing authorization of biosimilars, but the objective of the data gathered preauthorization is just to detect a potentially new safety signal not previously described for the originator. In any case, a robust pharmacovigilance and risk management plan should be in place that will allow continuous monitoring of the biosimilar's safety, in the same way as for any other biological medicine recently approved.