of biosimilar are also described. These requirements are based on previous clinical experience with innovative medicines of the same therapeutic class. The complexity of the molecule and the knowledge of its mechanism of action have also been considered. Then the requirements for a biosimilar of a small simple molecule with wide clinical experience such as insulin are simple (since it is a relatively small molecule, nonglycosylated, easy to characterize, and with a well-known mechanism of action), and it is possible that comparability PK/PD studies are sufficient for marketing authorization. Studies required for a biosimilar erythropoietin are more complex and even more so for a monoclonal antibody. Extrapolation of indications is relatively easily done for erythropoietin and G-CSF (as both have a well-known mechanism of action and their effect in different indications is mediated by the same receptor), but it is much more complicated in the case of monoclonal antibodies. These annexes are subject to frequent revision as more experience is gained in the authorization and use of biosimilars.

Other guidelines should also be considered when developing a biosimilar medicinal product, although they are not specific for biosimilars, that is, immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA, 2006) and of monoclonal antibodies intended for *in vivo* clinical use (EMA, 2010).

15.4 THE FIRST DECADE

To date, more than 20 biosimilars have been approved in Europe, including different active ingredients: somatropin, filgrastim (G-CSF), epoetin, follitropin alfa, insulin, and the first monoclonal antibody, infliximab. A few others have been assessed through the centralized procedure that did not receive a positive opinion. More biosimilar medicines are under development, such as pegylated filgrastim and monoclonal antibodies adalimumab and rituximab.

The availability of biosimilars has resulted in a substantial reduction in the price of biologics in the same therapeutic class, as not only their price is lower than the price of the reference product but also their emergence has resulted in a price reduction from innovators. In Norway, epoetin and filgrastim biosimilars are included in a national tender for drugs used in hospitals, in which prices can be reduced by up to 89% (GaBI online, 2015a).

The pattern of use or market access for biosimilars has been variable in different EU countries, mirroring somehow the countries' previous experience with the use of generics. A wide use of biosimilars in Germany has resulted in significant savings for their health care system (IMS Institute, 2014). In other EU countries (e.g., Spain), the initial market access was low, but, after years of experience and as a consequence of the economic crisis, the use of biosimilars is increasing. Certainly, the Norwegian experience with a recent tender for infliximab is very interesting (GaBI online, 2015b). Orion Pharma had proposed a 72% price reduction for the infliximab biosimilar Remsima (69% lower cost than the price for Remicade), resulting in substantial savings for the hospital budget and the health care system. Patients receiving Remicade are expected to remain on this treatment until more data on switching to the biosimilar can be provided (Stanton, 2013).

It is clear that with more experience in the assessment and clinical use of biosimilars, their uptake is steadily increasing, even in countries initially reluctant to