(recombinant) process and was approved by the FDA in 1982 (White Junod, 2009). Similarly, growth hormone from human origin (the pituitary gland from cadavers) was obtained in 1956 and was used in patients with growth hormone deficiency at the end of that decade (Ayyar, 2011). The first recombinant growth hormone was obtained in 1981. The production of these therapeutic proteins from biotechnological processes solved critical problems associated with their equivalents from biological origin, such as immunogenicity or hypersensitivity or infectious disease transmission (e.g., Creutzfeldt-Jakob disease).

Advances in molecular biology and genetic engineering allowed a large and reliable source of these medicines from microbial cell cultures (bacteria, yeast) or mammalian cell lines. Modified versions of these proteins (e.g., pegylated interferon, B-domain deleted factor VIII, insulin glargine) or fusion proteins (e.g., etanercept, abatacept) also became available. Recombinant enzymes and certain monoclonal antibodies are currently the standard of care for many diseases and have also allowed the treatment of rare disorders (e.g., alglucosidase alfa, human C1-inhibitor, eculizumab). Biotechnology drugs have a clearly established efficacy and safety profile as they are the treatment option for many chronic conditions and no transmission of infectious disease has ever been reported even when materials from biological origin are used in their production. More biotechnology-derived medicines are becoming available, and monoclonal antibodies are used in many different therapeutic areas, some providing an entirely novel approach to the treatment of their respective indications (e.g., rheumatoid arthritis, oncology, macular degeneration, or lupus), including rare orphan diseases (e.g., eculizumab for paroxysmal nocturnal hemoglobinuria).

The main drawback of biotechnology-derived medicinal products is possibly their high price, which is posing a challenge for the sustainability of health care systems. Many complex factors contribute to the high cost of biotech drugs (the production process and its control are only a small part of it), but, as with generic medicines, the legislation on similar biological medicinal products (or biosimilars) has the same goal—that is, to try to reduce the cost of clinical treatments based on biological and biotech drugs by introducing market competition. After a decade of experience in the EU with this regulation, more than 20 biosimilar medicines have been approved so far (including the first monoclonal antibodies), some of them widely used. However, some of the initial challenges for their introduction remain and will be discussed here. Guidelines for biosimilar development were first published in 2005 and have been updated according to the experience gained. The main concepts in these guidelines and rationale are also described.

15.2 REGULATORY FRAMEWORK IN THE EUROPEAN UNION

The EU regulatory region has been the pioneer in developing requirements for the approval of biosimilars—that is, those developed as equivalent to other biologics on the market and whose data protection period is over. Given the complexity and heterogeneity of biological medicines, specific legislation has been developed (EC, 2004: Directives 2003/63/EC and 2004/27/EC). Directives are European laws that establish basic principles but leave their implementation to national governments