and safety profile for the reference product. The type and amount of additional data should comply with the relevant criteria stated in Annex I and the related detailed guidelines.

15.3 NOTES FOR GUIDANCE OR GUIDELINES

The EMA has developed three main guidelines for biosimilars: a general guide describing the basis for authorization of biosimilars (EMA, 2014); a quality guideline describing the data required on production and control of a biosimilar and emphasizing comparability studies against the reference medicine (EMA, 2012); and guidance on the nonclinical and clinical studies to demonstrate comparability (EMA, 2015). The last-named includes a series of annexes with specific requirements for certain biosimilar medicinal products (e.g., erythropoietin, filgrastim, insulin, monoclonal antibodies). The three general guidelines were initially published in 2005 and have been recently reviewed after a decade of experience in the assessment, marketing, and use of biosimilars. A brief summary of the updated guidelines is provided below.

15.3.1 Guideline on Similar Biological Products

In the updated guideline, the concept of similar biological medicinal products has been introduced, and the basic principles to be applied for the development of biosimilars have been outlined (EMA, 2014).

Although the concept of biosimilarity is applicable to any biological medicinal product, this approach has been successfully used mainly for recombinant proteins as they present less heterogeneity than products obtained by extraction from biological sources (e.g., from tissues or fluids) and can be well characterized. The first biosimilar of enoxaparin sodium has been recently authorized by the EMA and others are under development.

The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product, and for protein active substances the amino acid sequence is expected to be the same. Any differences in strength, pharmaceutical form, or formulation will require justification or additional studies to support comparability. The changes aimed at improving efficacy are not compatible with establishing biosimilarity.

The chosen reference medicinal product must be authorized in the European Economic Area (EEA) (based on a complete dossier under Article 8 of Directive 2001/83/EC as amended) and must be the same for the entire comparability program, that is, quality, safety, and efficacy studies. However, with the aim of facilitating the global development of biosimilars, the updated version of the guideline considers the possibility to compare the biosimilar in certain clinical studies and in some nonclinical studies with a comparator authorized by a regulatory authority with similar scientific and regulatory standards as EMA (e.g., ICH countries), as long as comparability at the quality level (physicochemical structure and biological activity) has been established between the biosimilar and the reference product sourced from both EEA and non-EEA countries.