marketing authorization dossier for a biosimilar medicine is the same as for any other biotech drug but should also include all quality comparative studies between the reference product and the biosimilar.

Documentation regarding the development and manufacturing process for biosimilars should cover two distinct but complementary aspects: first, molecular characteristics and quality specifications (comparable to the reference product) and, second, the consistency of the specific production process of the biosimilar.

The comparability exercise should be comprehensive and should show that the biosimilar has a quality profile very similar to the reference medicinal product. It should include side-by-side comparative studies of several batches of the reference and the biosimilar using state-of-the-art, sensitive methods to determine not only the similarities but also the possible differences in quality attributes. The comparability study includes the evaluation of the physicochemical parameters (composition, physical properties, primary, and higher-order structures), identification of variants of the molecule (including product-related substances), and analysis of biological activity. Any differences identified will have to be duly justified in light of their possible impact on the safety and efficacy of the product. To establish comparability, it is necessary to define acceptance criteria (quantitative whenever possible) whose relevance should be discussed, considering the number of batches of reference product analyzed, the quality parameter studied, and the test method used. In principle, these acceptance limits should not be broader than the range of variability of representative batches of the reference medicine.

As described above, the production process and control of a biosimilar are subject to optimization and evolution, as it is the case with any other medicine, including the reference medicinal product. Any subsequent changes in the manufacturing process of the biosimilar (active substance and/or finished product) will have to follow a comparability assessment (as described in Guideline ICH Q5E) (EMA, 2003), and it will be assessed following the same rules as for any other biological medicinal product. If any of those changes result in significant molecular differences that may impact the approved efficacy and safety profile, additional studies may be required.

15.3.3 Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical and Clinical Issues

This guideline came into force on June 1, 2006, and has also been reviewed recently (EMA, 2015). It describes the general principles for the nonclinical and clinical development and evaluation of applications for marketing authorization of biosimilars containing recombinant proteins as active ingredients (although these principles could be applied to other biological products as well).

The nonclinical section addresses the pharmacotoxicological assessment. The clinical section describes the requirements for pharmacokinetic (PK), pharmacodynamic (PD), efficacy studies, and clinical safety and pharmacovigilance studies (including immunogenicity and the risk management plan).