through their respective national laws or regulations. In contrast, Notes for Guidance or guidelines include recommendations based on scientific knowledge in a particular area and, therefore, are subject to periodic review to adapt to scientific progress or changes in a particular regulatory strategy. A different approach from that described in those recommendations may be possible if adequately justified. Guidelines aim to provide a basis for practical harmonization among EU countries on how to interpret and apply the requirements to demonstrate the quality, safety, and efficacy set out in EU directives. Also, they help ensure that applications for marketing authorization are presented in a way that will be recognized as valid by the EMA. Specific Directives and Guidelines applicable to biosimilar medicines in the EU are described briefly in the following.

Directive 2003/63/EC, published on June 27, 2003, amending Directive 2001/83/EC, defines (in *Part II: Specific marketing authorization dossiers and requirements*) the concept of "similar biological medicinal products," commonly called "biosimilars" (EC, 2003). A biosimilar, as has been noted in earlier chapters, is a biological medicinal product that has been developed as equivalent to an other biological medicine already marketed (called "reference product"). The active ingredient of the biosimilar and the reference medicinal product is essentially the same, although there may be slight differences depending on the complexity of its structure and the method of production. Both the reference medicine and the biosimilar have a natural variability inherent to all biological medicinal products. A biosimilar medicinal product is authorized when it has been concluded, based on comparable data available, that those small differences between the two have no significant impact on safety and efficacy.

Biosimilars are normally authorized years after the reference product has been on the market (as the period of data protection has expired) and are used to treat the same disease and use the same dose as the reference medicinal product. Therefore, the large experience in terms of efficacy and safety from the reference product can be used for the development of a biosimilar medicinal product.

This Directive recognizes that, for biological medicines, it is possible that the information required for "essentially similar medicinal products" (generics) does not allow demonstration of the similar nature of two biological medicinal products, and, therefore, additional data should be provided, in particular, the toxicological and clinical profile. The type and amount of additional data (i.e., toxicological and relevant nonclinical and clinical data) shall be determined case by case, taking into account all relevant scientific guidelines and the special characteristics of each drug. If the originally authorized medicinal product has more than one clinical indication, the extrapolation of efficacy and safety of the biosimilar medicine should be justified or, if necessary, demonstrated separately for each of the claimed indications.

Directive 2004/27/EC, published on April 30, 2004, amends Directive 2001/83/EC and also considers that biosimilar medicinal products do not usually meet all the conditions to be considered as generic drugs, mainly due to the characteristics of the manufacturing process, the raw materials used, molecular characteristics, and therapeutic modes of action (EC, 2004). Then the results of the appropriate preclinical testing or clinical trials should be provided to establish a similar efficacy