adopt their use. Also, innovator companies have realized the potentially enormous benefit of certain biologics with a very large market and a safe and reduced clinical program. Therefore, they are also getting onboard for biosimilar development.

15.5 REMAINING CHALLENGES

Even after a decade of experience with marketing authorization and clinical experience in the EU with biosimilars, certain challenges still remain in certain countries for a wider use of biosimilars. Among those cultural issues (e.g., previous experience with the use of generics), pricing strategies from originators have played an important role, but the most debated are still related to extrapolation of indications, pharmacovigilance and traceability, and interchangeability and substitution. These strategies are considered further in the following section.

15.5.1 Interpretation of Differences and Extrapolation of Therapeutic Indications

Biosimilars are not identical to their reference medicine due to the complexity of the molecular structure (in contrast to chemicals and their generics). Additionally, the frequently cited paradigm "the process is the product" may leave prescribers and patients concerned about the interpretation of minor differences between the two molecules (e.g., in glycosylation pattern) and any remaining uncertainties with respect to efficacy and safety of the biosimilar as they are approved on a reduced clinical development.

Medicinal products in general are subject to changes in their manufacturing process throughout their life cycle. For biologics, some of these modifications can be relatively minor (e.g., change in a test method, tightening of a specification), and others may result in detectable molecular changes (e.g., elimination of a cell culture reagent can result in a modification of the glycosylation pattern) or in the product purity profile (e.g., different distribution of charge variants, level of aggregates, etc.). The assessment of these modifications is based on comparability studies between batches from the medicinal product before and after the change is introduced, and in many cases these quality data (i.e., analysis of physicochemical structure, biological activity, and purity using state-of-the-art methods) have been considered sufficient to support the change and keep the medicinal product on the market under the same conditions as when it was approved (EMA, 2003). If clear differences are observed, additional *in vitro* characterization or PK/PD data may be required, as will supplementary pharmacovigilance activities to ensure that no new safety signals are identified but in any case a new clinical development (i.e., demonstration of a positive benefit/risk in all approved indications) has been requested. Therefore, regulators have learned from extensive experience in assessing such changes and judging their potential impact on efficacy and safety. Pharmacovigilance of the medicinal product after the change was introduced has also added knowledge from those regulatory decisions. The same tools and rationale are used for biosimilars. That is, assessment of any difference in product quality when compared to the reference medicinal product in the context of the complexity of the molecule and knowledge of its mechanism