On the other hand, one must realize that granting the status of "interchangeability" between two drugs will automatically lead to subsequent practices regarding switching and substitution. Before substitution of small molecules can be considered, regulators must declare that sufficient similarity of the safety and efficacy of the drug products has been demonstrated. With small-molecule, chemical drugs, *sufficient similarity* is usually based on a clearly defined, rigorous statement of the *bioequivalence* between the pharmacokinetic profiles of the contrasted drug products. The comparison typically involves the generic and the reference formulation. Thus, clear, simple regulatory requirements and criteria have been declared for establishing the bioequivalence between a small-molecule, generic formulation and a reference product as set out in regulatory guidances (EMA, 2010; FDA, 2001, 2013).

Within the context of biological drugs, this issue is much more complicated. For instance, biological drugs have much higher molecular weights with convoluted structures, they are produced biotechnologically by host cell lines, and they are less stable and have complex physicochemical properties. Their properties are susceptible to small differences in the environment (e.g., temperature, light, oxygen) and the manufacturing process. During their production processes, there is a possibility of contaminants, which can be difficult to detect and, at times, impossible to remove. Even though techniques for the characterization of biologicals have been very much advanced and lead to analytical fingerprinting of the molecule (see Chapter 2 in this book), differences between the biosimilar and reference product do exist and are either detectable or may remain elusive as exemplified in the European Public Assessment Reports (EPAR, EMA website) of approved biosimilars. The most difficult issue involves learning which differences may be clinically relevant. In addition, biologicals are immunogenic, and this property may be impacted through frequent switching between highly similar products. Indeed, immunological pathways indicate that switching a stable patient to a strongly related molecule may cause a challenge to the immunologically tolerized state versus the first therapeutic. Well-established tolerization mechanisms include clonal deletion, receptor editing, clonal anergy, blockade of memory response, and competitive tolerance (Stewart et al., 1997). Immunological response to biological therapeutics varies between patients. Select patient subsets develop antidrug antibodies (ADAs), with clinical impact ranging from no impact at all to secondary loss of response. The immune response to biologicals is a dynamic process, and, importantly, ADAs may develop and disappear over time. Whether a stable patient subjected to a nonmedical switch between the reference and a biosimilar (or vice versa) can maintain tolerance is not known.

As a consequence of the differing features of small-molecule generics and biosimilars, regulatory considerations and approaches to the interchangeability of two products are very different after their bioequivalence has been declared or when their biosimilarity has been stated.

As noted earlier, a regulatory statement of bioequivalence of a small-molecule generic formulation to a reference product generally implies their interchangeability within patients. In contrast, a regulatory declaration of biosimilarity between a biosimilar and its reference product does *not* imply interchangeability; the two conditions are sharply different. Therefore, clear criteria need to be set to grant the property "interchangeability," and in particular, conditions for its application in a