of the biosimilar. After side-by-side characterizations of structure and function, and comparative nonclinical studies are completed, a tailored clinical program is planned. The comparative clinical program usually includes studies to investigate clinical pharmacokinetics/pharmacodynamics (PK/PD), clinical efficacy/safety, and immunogenicity between the biosimilar and the RBD. The purpose of the clinical program is not to reestablish the efficacy and safety profile of the biosimilar, since that has been fully established by the reference product and has been assessed at the time for the marketing application of the RBD. Rather, the demonstration of similarity at the analytical and biological level allows a regulatory link to be created that forms the bridge between the innovator's clinical data and the biosimilar product. Thus, the goal of the clinical program is to rule out clinically meaningful differences by resolving the residual uncertainties that remain due to small differences observed during analytical or biological testing or due to the technological limitations of the analytical and biological testing methodologies. If clinically meaningful differences are not observed in well-designed clinical studies, a final determination of similarity can be made and the extrapolation of indications can be considered.

9.3.2 Primary Clinical PK/PD Studies

The first clinical studies that should be conducted are the comparative human PK studies and, when feasible, comparative human PD studies. Comparative PK/PD studies can be used to confirm comparability that has been established through the structural and functional studies, to justify the reduction of subsequent clinical studies (e.g., insulin), and to establish evidence for extrapolation of indications (e.g., cancer vs. RA; adult vs. pediatric). It is not necessary to study the biosimilar in every indication that has been authorized. However, separate comparative PK studies may be required to bridge multiple distinct conditions. The number of studies required depends both on the degree of similarity between the biosimilar and the RBD [ascertained from the chemistry, manufacturing, and control (CMC) data] and on the indications for which the biosimilar is proposed. The design of the comparative PK studies depends on various factors, including clinical context, safety profiles, and PK characteristics of the RBD (target-mediated disposition, linear or nonlinear PK, time dependency, half-life, etc.).

The comparative PK studies should be conducted in a setting that is reflective of the clinical situation and is sensitive enough to detect potential differences if they exist. The single-dose crossover design (short half-life) is generally regarded as the most sensitive assessment of comparative bioavailability and may be conducted in healthy volunteers. However, healthy volunteers may not always adequately reflect the PK parameters in the patient population, since host factors such as receptor expression, receptor internalization rate, and patient status can affect the disposition and clearance of biologics (e.g. target-mediated disposition for mAbs). In addition, route of administration is an important factor to consider in the design and conduct of comparative PK studies. It is highly recommended that the PK of the biosimilar be compared to the RBD using a route that requires an absorption step if such a route is used by the RBD. For biologics, the subcutaneous (sc) route of administration is more discriminative than the intravenous