clinically meaningful differences." Biosimilar sponsors should consult each individual regulatory agency prior to conducting such trials.

The most sensitive study endpoint within a sensitive population should be considered in order to improve the detection of potential differences between products. Potentially, a study could use a clinically relevant and sensitive study endpoint that is different from the innovator's original primary endpoint(s). For instance, the choice of ACR20 versus DAS28 has been debated for the rheumatoid arthritis (RA) population (Dougados et al., 2009), while using ORR or progression-free survival (PFS) as the primary endpoint, instead of overall survival (OS), in oncology trials could be considered for biosimilars (Ahn et al., 2011). Finally, a new surrogate or a more sensitive clinical endpoint or different time points of analysis for traditional study endpoints could all be considered acceptable depending on the proposal (EMA, 2015).

Regardless of the chosen endpoint, clinical studies should demonstrate comparable safety and efficacy profiles. Any differences detected between the efficacy of the biosimilar and the RBD should always be discussed as to whether they are clinically relevant. Generally, the aim of clinical trials is to address minor differences observed during the comparability exercises and to demonstrate that the clinical performances of the biosimilar and the RBD are comparable. However, *it is important to note that clinical data cannot be used to justify substantial differences in quality attributes.*

Extrapolation of efficacy is acceptable when a biosimilar has demonstrated high comparability to the RBD in physicochemical and functional characteristics; in nonclinical studies obtained from relevant species; and in clinical PK/PD and clinical efficacy studies in population sensitive enough to show differences, and if all concerns with respect to the principle of indication extrapolation have been addressed.

### 9.3.4 Safety and Immunogenicity

For a particular product, safety profiles may differ among the various indications due to a number of factors. For example, therapeutic dose, concurrent conditions, and/or concomitant medicines may have an impact. Although there are concerns with the practice of extrapolating safety profiles among indications, safety comparability demonstrated in an indication with high sensitivity to detect differences may support extrapolation to other indications.

Most biologics induce some level of antidrug antibodies (ADAs), and these ADAs may have an undesirable clinical effect on pharmacokinetics, efficacy, and/or safety. Particularly, a change in the production process of a biologic might influence the immunogenic potential of that biologic (Shankar et al., 2006). Unwanted immunogenicity is currently difficult to predict from the analytical and nonclinical data in terms of incidence, characteristics, clinical consequences, and significance. Immunogenicity evaluation should be part of clinical efficacy and safety studies for biosimilars. To support extrapolation of indications, clinical studies should be carefully planned, and experimental data should be systematically collected from a sufficiently large number of patients and sufficient study duration in at least one clinical study to characterize the variability in immunogenicity response. The biosimilar has to demonstrate that immunogenicity is not increased and that the type of immunogenicity is not changed in a sensitive population.