Monitoring of ADA during Phase 1 and Phase 3 studies has enabled assessment of potential differences in the incidence and magnitude of ADA formation on sensitive PK parameters and on (less sensitive) clinical efficacy and safety endpoints. While correlation with PD endpoints has been important for cytokine products, often there are rather limited PD correlates for therapeutic monoclonal antibodies. An additional opportunity of 6- and 12-month duration therapeutic equivalence studies is the comparative evaluation of the dynamics of antibody formation in direct relation to clinical response and to steady-state drug concentration.

FDA guidance recommends that clinical evidence of comparative immunogenicity should be generated in addition to comparative PK/PD, most likely in a separate clinical study. Thus, the current practice is to include immunogenicity-related endpoints in separate studies that evaluate: (1) comparative PK (and PD if suitable markers are available); *and* (2) therapeutic equivalence during repeated administration for 6–12 months. The FDA has, in addition, required evaluation of incremental ADA formation following transition of subjects from the reference medicinal product to the biosimilar, for example, during an open-label extension period of the therapeutic equivalence study.

12.21 COMPARATIVE PK STUDIES

Comparative, parallel-group, PK studies in healthy volunteers and patients, powered to demonstrate bioequivalence, have yielded valuable information on relative immunogenicity for different therapeutic monoclonal antibody products, including adalimumab (Kaur et al., 2014), trastuzumab (Yin et al., 2014), and rituximab (Florez et al., 2014).

In the case of adalimumab, a single subcutaneous administration to healthy volunteers induced detectable ADA formation in 50%–70% of subjects. This enabled a correlation of the magnitude of the ADA response with primary and secondary PK parameters—which, arguably, represent the most sensitive clinical measures of an impact of ADA formation for adalimumab. Thus, for products for which there is an identified risk of clinical impactful immunogenicity associated with altered PK, correlation of ADA formation with PK parameters in a comparative PK study could enable assessment of the relative clinically impactful immunogenicity of biosimilar candidate with the reference product.

Neither trastuzumab nor rituximab was found to induce a detectable ADA response in these comparative PK studies; and bioequivalence was established from the highly similar PK parameters between the biosimilar and reference versions.

The primary statistical analysis for the comparative PK study via subcutaneous administration should include C_{max}, and AUC0-infinity as primary endpoints; $T_{1/2}$ should also be included, as well as C_{trough} for a repeated administration dose schedule. A secondary descriptive analysis would then compare relevant PK parameters for the ADA positive versus ADA negative subjects, and upper- versus lower quartile ADA titer subpopulations, in each treatment group; supportive graphical displays (e.g., scatterplots) could be included to illustrate the distribution of individual values in the respective treatment groups/subpopulations.