(C_t—concentration at the last measurable time point—divided by k_{el}—elimination rate constant) is calculated based on an appropriate method. C_{max} should be determined from the data without interpolation. For intravenous studies, $AUC_{0-\infty}$ will be considered the primary end point. For subcutaneous studies, C_{max} and AUC will be considered coprimary study end points. For multiple-dose studies, the measurement of total exposure should be the area under the concentration–time profile from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the length of the dosing interval, and this is considered the primary end point. The steady-state $C_{trough\ ss}$ should be measured at the end of a dosing interval before initiating the next dose and the C_{max} and these are considered secondary end points. Population PK data will not provide an adequate assessment for PK similarity.

3.8.5.7 PD measures In certain circumstances, human PK and PD data that demonstrate similar exposure and response between a proposed biosimilar product and the reference product may be sufficient to assess completely clinically meaningful differences between the products. This would be based on similar PDs using a PD measure that reflects the MOA in cases where the PD measure has a wide dynamic range over the range of drug concentrations achieved during the PK study. In such instances, a full evaluation of safety and immunogenicity would still be necessary, either before or after approval. When human PD data in a PK/PD study are insufficient to assess completely for clinically meaningful differences, obtaining such data may support a more targeted approach for the collection of subsequent clinical safety and effectiveness data. The selection of appropriate time points and durations for the measure of PD markers will depend on the characteristics of the PD markers (e.g., timing of PD response with respect to product administration based on the half-life of the product and the anticipated duration of effect). When a PD response lags after initiation of product administration, it may be important to study multiple-dose and steady-state conditions, especially if the proposed therapy is intended for long-term use. Comparison of the PD markers between the proposed biosimilar product and the reference product should be by determination of the area under the effect curve. If only one PD measurement is available due to the characteristics of the PD marker, it should be linked to a simultaneous drug concentration measurement, and this should be used as a basis for comparison between products.

The use of a single, scientifically acceptable, established PD marker as described above, or a composite of more than one relevant PD markers, can reduce residual uncertainty with respect to clinically meaningful differences between products and significantly add to the overall demonstration of biosimilarity. Using broader panels of biomarkers (e.g., by conducting a protein or an mRNA microarray analysis) that capture multiple pharmacological effects of the product may be of additional value.