When available and appropriate, clinical end points in clinical pharmacology studies may also provide useful information about the presence of clinically meaningful differences between two products.

3.8.5.8 Defining the appropriate PD time profile The optimal sampling strategy for determining PD measures may differ from the strategy used for PK measures. For PK sampling, frequent sampling at early time points following product administration with decreased frequency later is generally the most effective to characterize the concentration–time profile. However, the PD–time profile may not mirror the PK–time profile. In such cases, the PD sampling should be well justified. When both PK and PD data are to be obtained during a clinical pharmacology study, the sampling strategy should be optimized for both PK and PD measures.

3.8.5.9 Statistical comparison of PK and PD results The assessment of clinical pharmacology similarity of a proposed biosimilar product and the reference product in PK and PD studies is based on the statistical evaluation. The recommended clinical pharmacology similarity assessment relies on (a) a criterion to allow the comparison, (b) a confidence interval for the criterion, and (c) an acceptable limit. The Agency recommends that log transformation of the exposure measures be performed before the statistical analysis. Sponsors should use an average equivalence statistical approach to compare PK and PD parameters for both replicate and nonreplicate design studies. This approach involves a calculation of a 90% confidence interval for the ratio between the means of the parameters of the proposed biosimilar product and the reference product. To establish PK and/or PD similarity, the calculated confidence interval should fall within an acceptable limit. The selection of the confidence interval and the acceptable limits may vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio may be 80%–125%; however, this is not a default range, and the sponsor should justify the limits selected for the proposed biosimilar product. There may be situations in which the results of the PK and/or the PD study fall outside the predefined limits. Although such results may suggest the existence of underlying differences between the proposed biosimilar product and the reference product that may preclude development under the 351(k) pathway, the Agency encourages sponsors to analyze and explain such findings. If such differences do not translate into clinically meaningful differences and the safety, the purity, and the potency of the product are not affected, it may be possible to continue the development under the 351(k) pathway.

3.8.5.10 Utility of simulation tools Modeling and simulation tools can be useful when designing a PK and/or a PD study. For instance, such tools can contribute to the selection of an optimally informative dose or doses for evaluating PD similarity. When a biomarker-based comparison