study does not duplicate or substitute for the information provided by the other. Both PK studies and PD studies provide valuable information for assessing biosimilarity; and, therefore, as a scientific matter, comparative human PK studies and PD studies (where there is a relevant PD measure(s)) will be generally expected.

3.4.5.4.1 Human pharmacology data Human PK and PD profiles of a protein product cannot often be adequately predicted from functional assays and/or animal studies alone. Therefore, human PK and PD studies comparing a proposed product to the reference product are generally fundamental components in supporting a demonstration of biosimilarity. Both PK and PD studies (where there is a relevant PD measure(s)) will generally be expected to establish biosimilarity, unless a sponsor can scientifically justify that such a study is not needed. Even if relevant PD measures are not available, sensitive PD end points may be assessed if such assessment may help reduce residual uncertainty about biosimilarity.

Sponsors should provide a scientific justification for the selection of the human PK and PD study populations (e.g., patients versus healthy subjects) and parameters, taking into consideration the relevance and sensitivity of such population and parameters, the population and parameters studied for the licensure for the reference product, as well as the current knowledge of the intrasubject and intersubject variability of human PK and PD for the reference product. For example, comparative human PK and PD studies should use a population, a dose, and a route of administration that are adequately sensitive to allow for the detection of differences in PK and PD profiles. The FDA recommends that, to the extent possible, the sponsor selects PD measures that (a) are relevant to clinical outcomes (e.g., on mechanistic path of MOA or disease process related to effectiveness or safety); (b) are measurable for a sufficient period after dosing to ascertain the full PD response and with appropriate precision; and (c) have the sensitivity to detect clinically meaningful differences between the proposed product and the reference product. The use of multiple PD measures that assess different domains of activities may also be of value.

When there are established dose–response or systemic exposure–response relationships (response may be PD measures or clinical end points), it is important to select, whenever possible, a dose for a study on the steep part of the dose–response curve for the proposed product. Studying doses that are on the plateau of the dose–response curve is unlikely to detect clinically meaningful differences between the two products. Sponsors should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity.

A human PK study that demonstrates similar exposure (e.g., serum concentration over time) for the proposed product and the reference product