pathway for agency licensure of biological products that are demonstrated to be biosimilar to or interchangeable with an agency-licensed reference product. The term *biosimilarity* is defined in Section 351(i) of the PHSA to mean that the biological product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that there are "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." Under Section 351(k)(2) of the PHSA, a 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product (a biological product already licensed under Section 351(a) of the PHSA) based on data derived from analytical studies; animal studies; and a clinical study or clinical studies, including the assessment of immunogenicity and PK and PD, unless the Agency determines, in its discretion, that certain studies are unnecessary in a 351(k) application.

Clinical pharmacology studies are normally a critical part of demonstrating biosimilarity by supporting a demonstration that there are no clinically meaningful differences between the proposed biosimilar and the reference product. These studies provide the data that describe the degree of similarity in drug exposure between the proposed biosimilar and the reference product. In addition, clinical pharmacology studies often include PD end points (both therapeutic and toxic) and pharmacometric analysis to assess whether or not there are clinically meaningful differences between the proposed biosimilar and the reference product. If done well, they can add to the totality of the evidence, reduce residual uncertainty, and thus guide the need for the design of subsequent clinical testing to successfully support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data may be an important component of the scientific justification supporting extrapolation of clinical data to one or more additional conditions of use.

The types of clinical pharmacology studies to be conducted will depend on the residual uncertainties about biosimilarity that these studies are capable of addressing in the context of the overall program for biosimilar product development.

3.8.3 Critical considerations in the use of clinical pharmacology studies to support biosimilarity

Three key concepts, exposure and response assessment, evaluation of residual uncertainty, and assumptions about analytical quality and similarity, are especially relevant to the development of proposed biosimilar products.

3.8.3.1 Exposure and response assessment to support a demonstration of biosimilarity The objective of a well-designed clinical PK and PD