been identified, but the sponsor is encouraged to incorporate PD biomarkers that correlate well with drug exposure over a wide concentration range as these represent potentially orthogonal tests that may be supportive of clinical pharmacology similarity. When PD markers are not sensitive or specific enough to be used to assess for clinically meaningful differences, the derived PK parameters should be used as the primary basis for evaluating similarity from a clinical pharmacology perspective, and the PD markers may be used to augment the PK data.

- A combination of PK and PD similarities representing orthogonal biosimilarity may be an important assessment in demonstrating no clinically meaningful differences.

*3.8.3.2 Evaluation of residual uncertainty* In evaluating a sponsor's data to support a demonstration of biosimilarity, using a risk-based approach, the Agency will consider the totality of the data and the information submitted, including, for example, data from the structural and functional characterizations, nonclinical evaluations, human PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety and, when necessary, clinical effectiveness. These data should be collected in a stepwise manner. Especially pertinent to the Agency's clinical pharmacology evaluation is the clinical PK and PD data and safety data obtained in conjunction with the clinical pharmacology studies. The need for additional studies at each step in this progressive approach will be determined by the degree of residual uncertainty that remains at each step regarding the similarity of the products and whether or not the study can address these uncertainties.

*3.8.3.3 Assumptions about analytical quality and similarity* In a stepwise assessment of biosimilarity, extensive and robust comparative structural and functional studies (e.g., bioassays, binding assays, and studies of enzyme kinetics) should be performed to evaluate whether the proposed biosimilar product and the reference product are highly similar. A meaningful assessment depends on, among other things, the capabilities of available state-of-the-art analytical assays to assess, for example, the protein's molecular weight, HOS and PTMs, heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability. The sponsor should describe the capabilities and the limitations of the methods used in the analytical assessment.

An extensive analytical characterization may reveal differences between the proposed biosimilar product and the reference product. The type, the nature, and the extent of any differences between the two products should be clearly identified, and the potential effect of these differences should be addressed and supported by appropriate data. In some cases, additional studies may demonstrate that the identified difference is within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product. However, certain differences in