> high level of confidence in the analytical similarity of the proposed biosimilar and the reference product, and it would be appropriate for the sponsor to use a more targeted and selective approach to conducting animal and/or clinical studies to resolve residual uncertainty and support a demonstration of biosimilarity.

The outcome of the comparative analytical characterization should inform the next steps in the demonstration of biosimilarity.

3.8.4 Integrity of the bioanalytical methods used in PK and PD studies

When performing an evaluation of clinical pharmacology similarity, it is critical to use the appropriate bioanalytical methods to evaluate the PK and PD properties of a proposed biosimilar product and its reference product. Because of the complex molecular structure of biological products, conventional analytical methods used for chemical drugs may not be suitable for biological products. The bioanalytical methods used for PK and PD evaluations should be accurate, precise, specific, sensitive, and reproducible. The scientific requirements of bioanalytical methods have been described in a separate guidance document.

3.8.4.1 General PK assay considerations A sponsor should design or choose an assay based on a thorough understanding of the MOA and/or structural elements of the proposed biosimilar product and the reference product critical for activity. Analytical assays should be able to detect the active and/or the free product instead of the total product, particularly if binding to a soluble ligand is a necessary step for activity and clinical effect. The inability to develop such an assay should be supported with a justification as to why failure to detect free and/or active forms does not compromise the PK similarity assessment.

3.8.4.2 General PK and PD assay considerations Sponsors should make every effort to employ the most suitable assays and methodologies with the aim of obtaining data that are meaningful and reflective of the drug exposure, the biological activity, and/or the PD effect of the proposed biosimilar product and the reference product. Furthermore, the sponsor should provide a rationale for the choice of the assay and the relevance of the assay to drug activity in submissions to the Agency.

3.8.4.3 Specific assays Three types of assays are of particular importance for biosimilar product development: ligand-binding assays, concentration and activity assays, and PD assays.

3.8.4.3.1 Ligand-binding assays Currently, the concentration of most biological products in circulation is measured using ligand-binding