should be taken into account when assessing the robustness of the quality of data supporting biosimilarity and the need for additional information that may address residual uncertainties. Finally, functional assays are important in evaluating the occurrence of neutralizing antibodies in nonclinical and clinical studies.

3.7.5 Receptor-binding and immunochemical properties

When binding or immunochemical properties are part of the activity attributed to the protein product, analytical tests should be performed to characterize the proposed product in terms of these particular properties (e.g., if binding to a receptor is inherent to protein function, this property should be measured and used in comparative studies) (see ICH Q6B for additional details). Various methods such as surface plasmon resonance, microcalorimetry, or classical Scatchard analysis can provide information on the kinetics and the thermodynamics of binding. Such information can be related to the functional activity and the characterization of the proposed product's HOS.

3.7.6 Impurities

The sponsor should characterize, identify, and quantify impurities in the proposed product and the reference product, to the extent feasible. A risk-based assessment should be performed on any differences in process-related impurities identified between the proposed product and the reference product. If a comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary. However, if the manufacturing process used to produce the proposed product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary. See the ICH guidance for industry *S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, which states: "[i]t is preferable to rely on purification processes to remove impurities … rather than to establish a preclinical testing program for their qualification."

The use of the terms *product-* and *process-related impurities* is consistent with their use and meaning in ICH Q6B. Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachable, endotoxin, bioburden) should be evaluated. The process-related impurities in the proposed product are not expected to match those observed in the reference product. However, process-related impurities