the assay performance may differ depending on the specific PD assay. However, the general guiding principles for choosing PK assays (i.e., demonstration of specificity, reliability, and robustness) also apply to PD assays. Sponsors should provide supporting data for the choice of the assay and the justification of PD markers in submissions to the Agency.

3.8.4.4 Safety and immunogenicity In the context of this guidance, *immunogenicity* refers to an immune response to the biological product that may result in immune-mediated toxicity and/or lack of effectiveness. Safety and immunogenicity data from the clinical pharmacology studies should be collected and evaluated. The Agency recognizes that safety and immunogenicity data derived from these studies may need to be supplemented by additional evaluations either preapproval or postapproval. However, as part of their role in the overall assessment of biosimilarity, clinical pharmacology studies may sometimes suggest that there are clinically meaningful differences between the products that may inform the design and the details of additional investigations and/or clinical studies conducted to further investigate these potential differences. It is important to note that depending on the extent of such potential differences, it may not be appropriate for additional studies to be conducted in the context of a biosimilar development program.

Publicly available information on the safety and immunogenicity profile of a reference product should be considered when incorporating safety and immunogenicity measurements in the clinical pharmacology studies. For example, when a reference product is known to have the potential for immune-mediated toxicity, assays capable of detecting binding antibodies (and their neutralizing potential) should be developed in advance to analyze samples obtained from PK and PD studies, so that immunogenicity may be evaluated in real time. Generally, samples can be stored for future analysis if such assays are not yet developed. In either approach, sponsors should carefully consider assay confounders, such as the systemic presence of the proposed biosimilar or reference product. Recommendations for immunogenicity assay development have been described in a separate guidance document.

When evaluating data (e.g., safety, immunogenicity) collected during the PK and PD studies, sponsors should have an understanding of the time course of the appearance and the resolution of safety signals or immune responses. The PK profile of the proposed biosimilar product and/or the publicly available PK data for the reference product can be used to inform the duration of follow-up for safety signals or immunogenicity.

3.8.5 Developing clinical pharmacology data for supporting a demonstration of biosimilarity

Sponsors are encouraged to discuss the crucial aspects of their clinical pharmacology development plan with the Agency in the early stages of