sciences, may enhance the likelihood that a proposed product can be demonstrated to be highly similar to a reference product by better targeting the reference product's physicochemical and functional properties. In addition, advances in analytical sciences may enable detection and characterization of the differences between the protein products. These differences should be further assessed to understand the impact on product performance.

Despite improvements in analytical techniques, the current analytical methodology may not be able to detect or characterize all relevant structural and functional differences between the two protein products. A thorough understanding of each analytical method's limitations will be critical to a sponsor's successful identification of residual uncertainties and, in turn, to the design of subsequent testing. In addition, there may be an incomplete understanding of the relationship between a product's structural attributes and its clinical performance. Sponsors should use an appropriate analytical methodology that has adequate sensitivity and specificity to detect and characterize the differences between the proposed product and the reference product. Accordingly, the FDA encourages the use of widely available state-of-the-art technology.

In addition to a complete CMC data submission as required under Section 351(a) of the PHSA, an application submitted under Section 351(k) of the PHSA is needed to include data supporting the analytical similarity of the proposed biosimilar product to the reference product. The rationale for the analytical similarity assessment should be clearly described with consideration for the known quality attributes and performance characteristics of the specific reference product.

Comparative analytical data provide the foundation for a biosimilar development program and can influence decisions about the type and the amount of animal and clinical data needed to support a demonstration of biosimilarity. Such analytical data should be available early in product development and will permit more detailed discussion with the Agency because known quality attributes can be used to shape biosimilar development and to justify certain development decisions. Thus, in addition to the preliminary comparative analytical similarity data that should be submitted to support an initial advisory meeting, the FDA encourages sponsors to submit comprehensive analytical similarity data early in the development process: at the pre-IND stage, with the original IND submission, or with the submission of data from the initial clinical studies, such as PK and PD studies. The FDA will best be able to provide meaningful input on the extent and the scope of animal and additional clinical studies for a proposed biosimilar development program once the Agency has considered the analytical similarity data.

Extensive, robust comparative physicochemical and functional studies (these may include biological assays, binding assays, and enzyme