demonstrating that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (Section 7002(b)(3) of the Affordable Care Act and Section 351(i)(2)(B) of the PHSA). To support a demonstration of biosimilarity, the statute also requires a clinical study or studies (including the assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product, unless the FDA determines an element unnecessary (Section 7002(a)(2) of the Affordable Care Act and Section 351(k)(2)(A)(i)(I)(cc) of the PHSA). As a general matter, the FDA anticipates that the recommendations described in this guidance designed to demonstrate that the proposed product is highly similar to its reference product notwithstanding minor differences in clinically inactive components and to show that no clinically meaningful differences exist between the two products will provide data sufficient to demonstrate the safety, the purity, and the potency of the proposed product. The FDA recommends that sponsors identify which study or studies will provide data regarding no clinically meaningful differences prior to starting clinical studies.

The nature and the scope of the clinical study or studies will depend on the nature and the extent of residual uncertainty about biosimilarity after conducting structural and functional characterizations and, where relevant, animal studies. The frequency and the severity of safety risks and other safety and effectiveness considerations (e.g., the poor relationship between pharmacologic effects and effectiveness) for the reference product may also affect the design of the clinical program. The scope of the clinical program and the type of clinical studies (i.e., comparative human PK, PD, clinical immunogenicity, or clinical safety and effectiveness) should be scientifically justified by the sponsor.

As a scientific matter, the FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)). Note that a PD study may also incorporate PK measures (i.e., a combined PK/PD study) and a clinical immunogenicity assessment. In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. However, if residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products. PK and PD studies provide quite different types of information. In simple terms, a PK study measures how the body acts on a drug (how the drug is absorbed, distributed, metabolized, and eliminated), and a PD study measures how the drug acts on the body (typically assessing a measure related to the drug's biochemical and physiologic effects on the body). Therefore, one type of