the biosimilar development program. Some critical study design issues that should be discussed with the Agency are set forth below.

3.8.5.1 Study design To evaluate clinical PK and PD similarities for the development of proposed biosimilar products, two study designs are of particular relevance: crossover designs and parallel study designs.

3.8.5.1.1 Crossover design For PK similarity assessments, a single-dose, randomized, crossover study is generally the preferred design. A crossover study is recommended for a product with a short half-life (e.g., shorter than five days), a rapid PD response (e.g., onset, maximal effect, and disappearance in conjunction with drug exposure), and a low incidence of immunogenicity. This design is considered the most sensitive to assess PK similarity, and it can provide reliable estimates of differences in exposure with a minimum number of subjects. For PD similarity assessments, multiple doses may be appropriate when the PD effect is delayed or is otherwise not parallel to the single-dose drug PK profile. The time course of appearance and disappearance of immunogenicity and its relation to the washout period is an issue for consideration for studies using a crossover design.

3.8.5.1.2 Parallel design Many biological products have a long half-life and elicit immunogenic responses. A parallel group design is appropriate for products that have a long half-life or for which repeated exposures can lead to an increased immune response that can affect the PK and/or PD similarity assessments. This design is also appropriate for diseases that exhibit time-related changes associated with exposure to the drug.

3.8.5.2 Reference product The BPCI Act defines the reference product for a proposed biosimilar product as the single biological product licensed under Section 351(a) of the PHSA against which a proposed biosimilar product is evaluated in a 351(k) application. As a scientific matter, analytical studies and at least one clinical PK and, if appropriate, PD study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. However, a sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. If a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements of Section 351(k)(2)(A) of the PHSA, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies