may provide support for a demonstration of biosimilarity. A human PK study may be particularly useful when the exposure correlates with clinical safety and effectiveness. A human PD study that demonstrates a similar effect on a relevant PD measure related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) represents even stronger support for a biosimilarity determination.

In certain cases, establishing similar clinical PK, PD, and immunogenicity profiles may provide sufficient clinical data to support a conclusion that there are no clinically meaningful differences between the two products. PK and PD parameters are generally more sensitive than clinical efficacy end points in assessing the similarity of two products. For example, an effect on thyroid-stimulating hormone levels would provide a more sensitive comparison of two thyroxine products than an effect on clinical symptoms of euthyroidism.

In cases where there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary. For example, similar dose–response curves of the proposed product and the reference product on a relevant PD measure, combined with a similar human PK profile and clinical immunogenicity profile, could provide sufficient evidence to support a conclusion of no clinically meaningful differences. Even if there is still residual uncertainty about biosimilarity based on PK and PD results, establishing similar human PK and PD profiles may provide a scientific basis for a selective and targeted approach to subsequent clinical testing.

For PD studies using products with a short half-life (e.g., shorter than five days), a rapid PD response, and a low incidence of immunogenicity, a crossover design is appropriate, when feasible. For products with a longer half-life (e.g., more than five days), a parallel design will usually be needed. Sponsors should provide a scientific justification for the selection of study dose (e.g., one dose or multiple doses) and route of administration. The FDA recommends that sponsors consider the time it takes for a PD measure to change and the possibility of nonlinear PK. The FDA also encourages consideration of the role of modeling and simulation in designing comparative human PK and PD studies.

3.4.5.4.2 Clinical immunogenicity assessment The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and the severity of human immune responses. Immune responses may affect both the safety and the effectiveness of the product by, for example, altering PK, inducing anaphylaxis, or promoting the development of neutralizing antibodies that neutralize the product as well as its endogenous protein counterpart. Thus, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a fundamental element in