Biosimilars Info Sheet

Level 2: Regulatory and Scientific Concepts

Comparative Clinical Studies

Clinical studies are conducted with the goal of addressing any potential residual uncertainty and ensuring that there are no clinically meaningful differences between the proposed biosimilar product (also called biosimilar) and the reference product in terms of safety, purity, and potency (i.e., safety and effectiveness).

The nature and scope of the clinical study or studies will depend on the nature and extent of residual uncertainty about biosimilarity after conducting analytical and in vitro functional characterization.

What Kind of Clinical Studies Should Be Conducted to Address Residual Uncertainty?

- One or more clinical studies directly comparing the proposed biosimilar to the reference product are generally necessary. Examples include clinical pharmacology studies that evaluate pharmacokinetic (PK) similarity, pharmacodynamic (PD) similarity, and compare immunogenicity (i.e., safety), and comparative clinical studies (CCS) in patients with safety and efficacy assessments.
- The type and number of studies needed will depend on the nature of the proposed product. For example, an assessment of PK similarity may not be relevant for proposed biosimilars that have limited or undetectable systemic exposures, such as products administered to targeted tissues to achieve therapeutic effect locally (e.g., biologics administered to the eye by intravitreal injections). **Figure 2** also illustrates a monoclonal antibody reference product, a type of therapeutic protein (left panel), and a corresponding biosimilar (right panel), with diamonds of different colors on the biologics representing glycosylation sites with minor variations that occur during the manufacturing process.

What Type of Clinical Data Can Be Used to Evaluate Exposure, Efficacy, and Safety Between the Proposed Biosimilar and the Reference Product?

PK similarity data can be used to support similar exposure (**Figure 1**). If one or more suitable PD biomarkers are identified for use, the clinical development program may include comparative PK + PD + immunogenicity studies because PK and PD parameters are generally more sensitive than clinical efficacy endpoints in detecting differences between products. If one or more suitable PD biomarkers are not identified for use, the clinical development program may rely on a comparative PK and CCS approachproduct are carefully evaluated by FDA to ensure the biosimilar is highly similar to the reference product and meets FDA's high approval standards.

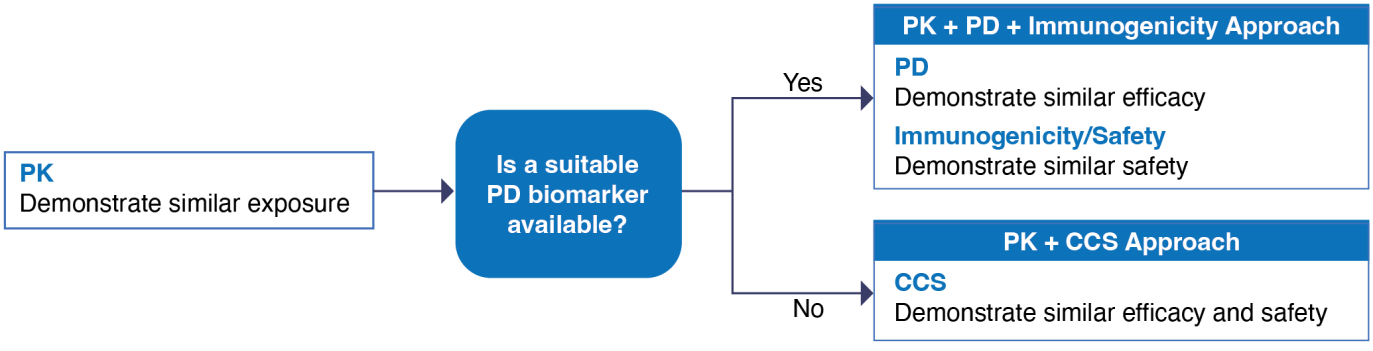


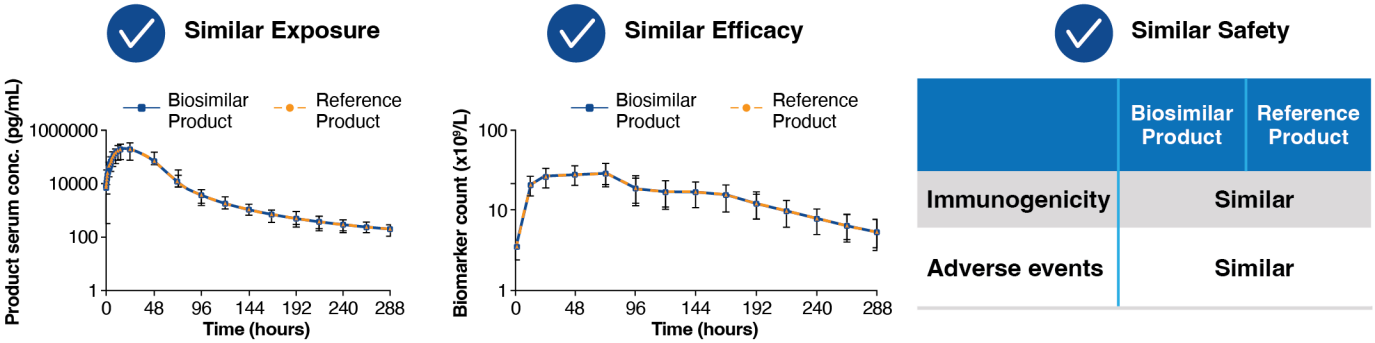
Figure 1: Clinical Study Strategy to Demonstrate Biosimilarity

Biosimilars Info Sheet

Level 1: Foundational Concepts

Example for PK + PD + Immunogenicity Approach

If one or more suitable PD biomarkers are available, the clinical data could include PK similarity data, PD similarity data, and comparative immunogenicity (i.e., safety) data to adequately demonstrate similar exposure, efficacy, and safety (**Figure 2**). Figure 2 demonstrates similar profiles were obtained for PK and PD, and the calculated 90% confidence interval of the geometric mean ratios for the PK and PD parameters fell within the pre-defined criteria used (80–125%).

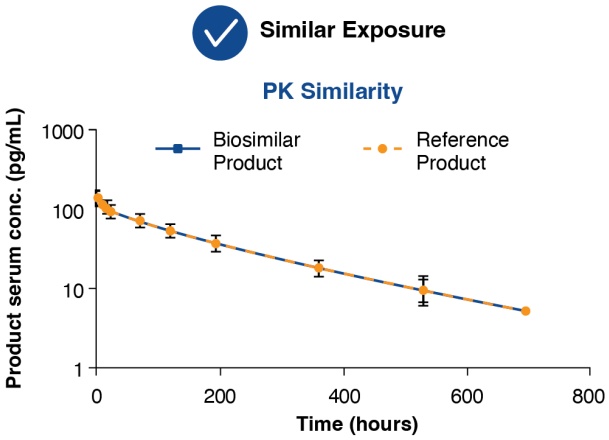


	Biosimilar Product	Reference Product
Immunogenicity	Similar	
Adverse events	Similar	

Figure 2: PK + PD + Immunogenicity Approach

Example for PK + CCS Approach

If a suitable PD biomarker is not available, the clinical data could include PK similarity data and CCS data to adequately demonstrate similar exposure, efficacy, and safety (**Figure 3**). The results shown in Figure 3 demonstrate a similar profile for PK, and the calculated 90% confidence interval (CI) of the geometric mean ratios for the PK parameters fell within the pre-defined criteria (80–125%). The CCS used an equivalence design, where similarity in efficacy was shown by statistically comparing response rates and similarity in safety was shown by descriptively comparing adverse events and immunogenicity.



Similar Efficacy

Similar Safety

CCS for Efficacy and Safety (Immunogenicity)

	Biosimilar Product	Reference Product
Response rate, n (%)	116/248 (46.8%)	129/256 (50.4%)
90% CI for risk ration estimate	0.7981-1.0796	
Equivalence margin	0.740-1.350	
Immunogenicity	Similar	
Adverse events	Similar	

Figure 3: PK + CCS Approach