Biosimilars Info Sheet

Level 2: Regulatory and Scientific Concepts

Biosimilar Product Quality Attributes

Physicochemical and Functional Molecular Properties

A biological product's molecular properties, also known as quality attributes, are physical, chemical, and biological characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product's quality. For biosimilar and interchangeable biosimilar products approved through the 351(k) abbreviated approval pathway, these attributes are carefully selected to support FDA's assessment whether a proposed biosimilar is highly similar in terms of its molecular structure, bioactivity, and purity to its reference product. A proposed biosimilar with similar structure and function to a reference product should behave like that reference product with respect to safety and effectiveness; therefore, these attributes are central to the totality of the evidence evaluated by FDA to determine biosimilarity. A manufacturer evaluates additional product attributes that further demonstrate their product meets all of FDA's rigorous quality standards for sterility, purity, and stability.

Selection of Quality Attributes

Important quality attributes are identified and evaluated based on the known or uncertain risk to impact the product's activity, pharmacokinetic and pharmacodynamic (PK/PD) profiles, safety, efficacy, or immunogenicity (**Figure 1**). If differences are detected between the biosimilar and reference product, additional information may be needed to determine whether the products are highly similar and have no clinically meaningful differences.

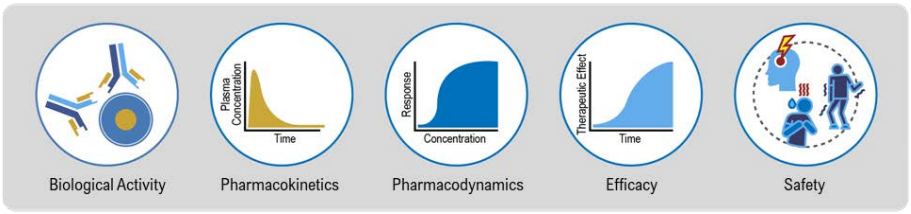

Figure 1: Quality Attributes May Impact One or More Aspects of Clinical Performance

Evaluating Quality Attributes and Performing the Comparative Analytical Assessment

For approval of a biosimilar, a manufacturer must demonstrate that relevant quality attributes of the proposed product are within acceptable limits defined, in part, by analyzing the same attributes for the reference product. An extensive battery of analytical studies are conducted to measure and directly compare the biosimilar and its reference product on each attribute, or to further ensure a product meets rigorous quality standards. **Figure 2** highlights examples of quality attributes that are frequently measured for insulin. Evaluation of these attributes provides foundational evidence regarding a biosimilar product's similarity to its reference product.

Molecular Structure	Bioactivity	Purity
Primary Structure	**Mitogenic Activity**	**Protein Concentration**
Amino acid sequence and mass	IR-A phosphorylation Mitogenic assay IR-A binding kinetics IGF1R binding kinetics	Activity and concentration in U/mL
Higher Order Structure	**Metabolic Activity**	**Other**
Conformation Post-translational modifications Hydrodynamic radius Disulfide bonds	IR-B phosphorylation Glucose uptake assay IR long form receptor binding kinetics IR autophosphorylation Adipogenesis assay Inhibition of stimulated lipolysis assay	Excipients (e.g., zinc content) Aggregates/High molecular weight proteins Isoelectric point
Product Variants		
Deamidation Glycerol ester Citric acid conjugate Acetylation		

Figure 2: Illustrative Product Quality Attributes for Insulin