

- Conditions of the use proposed in labeling have been previously licensed for the reference product.
- It has the same route of administration, dosage form, and strength as the reference product that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.
- 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.

2.2.3.1 *What interchangeable or interchangeability means*

- The biological product is biosimilar to the reference product.
- It can be expected to produce the same clinical result as the reference product in any given patient.
- For a product administered more than once, the safety and the reduced efficacy risks of alternating or switching are not greater than with repeated use of the reference product without alternating or switching. Note that the interchangeable product may be substituted for the reference product without the authorization of the healthcare provider.

2.2.3.2 *The totality-of-the-evidence approach*

- The totality-of-the-evidence approach describes a stepwise approach to evidence development, ensuring that development include only those elements necessary to address residual uncertainty.
- It introduces a concept that only after a thorough review of data from structural and functional analyses can the FDA provide meaningful advice on scope and extent of necessary animal and human testing.
- It explains the general expectations for human clinical trials.
 - At least one study will be expected (immunogenicity/pharmacokinetic/pharmacodynamic [PK-PD]).
 - Comparative safety and effectiveness data may be necessary if residual uncertainty exists.

A *biosimilar* product is a biological product that is licensed based on a showing that it is highly similar to an FDA-licensed biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness of the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.

An *interchangeable* biological product is biosimilar to an FDA-licensed reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the