Biosimilars Info Sheet

Level 2: Regulatory and Scientific Concepts

Comparative Analytical Assessment and Product Quality

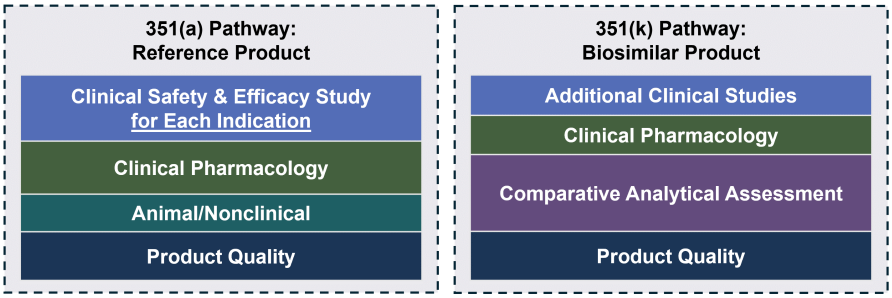

Figure 1: Reference Products and Biosimilar Products Are Approved Through Different Regulatory Approval Pathways

The goal of a biosimilar development program is to demonstrate that a proposed biosimilar is highly similar to and has no clinically meaningful differences from its reference product—not to independently establish the safety and effectiveness of the proposed product. This generally means that manufacturers do not need to conduct as many expensive and lengthy clinical trials for a biosimilar product that may have been needed for the reference product. In this way, the 351(k) pathway helps to reduce the time and cost of development without compromising safety and effectiveness because biosimilar and interchangeable biosimilar products are still subject to FDA's rigorous approval standards. For a reference product to be approved under the 351(a) pathway, the manufacturer is required to, among other things, provide FDA with all the data and information necessary to demonstrate that the proposed product is safe and effective for each of its proposed indications. When a proposed product meets the standards for biosimilarity under the 351(k) pathway, it means that the proposed product will have the same risks and benefits (i.e., safety and effectiveness) as its reference product. Using a totality-of-the-evidence approach, FDA considers all the available evidence needed to make a regulatory decision about the proposed product's biosimilarity to the licensed reference product (**Figure 1**). This body of evidence may include information from product quality assessments, clinical pharmacology, and additional clinical studies. However, the foundation of this evaluation is the comparative analytical assessment. Why? Analytical studies are generally much more sensitive than clinical studies in detecting differences between products.

Comparative Analytical Assessment Basics

The comparative analytical assessment comprises a comprehensive battery of structural (i.e., physicochemical) and functional (i.e., biological) analytical techniques. These highly sensitive assays help provide information and assurance about the identity, quality, safety, purity, and potency of the proposed biosimilar in comparison to the reference product. The confidence in the comparative analytical assessment is based on the principle that a biosimilar product with similar structure and function as the reference product should behave like the reference product clinically. Therefore, a product demonstrated to be analytically highly similar to the reference product is expected to be as safe and effective as the reference product.

Quality Attributes

Numerous characteristics, or quality attributes, of a reference product and proposed biosimilar product are evaluated as part of a comprehensive comparative analytical assessment. Biosimilar manufacturers identify quality attributes to include in the comparative analytical assessment based on available information in the public domain and analyzing multiple lots of the reference product. Quality attributes are assessed based on the potential impact of an attribute on the biosimilar or reference product's activity, pharmacokinetic/pharmacodynamic (PK/PD) profiles, safety, efficacy, or immunogenicity (**Figure 2**). A quality attribute is a physical, chemical, or biological property or characteristic of a drug substance that should be within an appropriate limit, range, or distribution to ensure the desired product quality and clinical performance.

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FDA pays particularly close attention to a critical group of these quality attributes in review of biosimilar product applications. These attributes can be qualitative or quantitative; it should be noted that an attribute can be critical even if not amenable to quantitative analysis. For example, the primary structure of a protein is a qualitative attribute that is imperative to the function of a proposed biosimilar product. A manufacturer also evaluates additional attributes that demonstrate their biosimilar product meets all of FDA's rigorous quality standards for sterility, purity, and stability.

Comparison of a Biosimilar Product to the Reference Product

Manufacturers conduct a head-to-head comparison of the proposed biosimilar product's quality attributes against the reference products in the comparative analytical assessment (**Figure 3**). To increase confidence in the assessment of a quality attribute, the use of orthogonal methods—independent ways to measure the same attribute—are considered a best practice for the comparative analytical assessment. The comparison between the reference product and the proposed biosimilar product also includes product-related impurities, including molecular variants of the desired biological product (e.g., aggregates, degradation products). Based on the results of analytical studies, the sponsor may have an appropriate scientific basis for a selective and targeted approach to subsequent clinical studies to support a demonstration of biosimilarity. FDA evaluates the comparative analytical assessment as the foundation of any biosimilar program and examines the complete package of data submitted by biosimilar manufacturers in their application to ensure that a proposed biosimilar product is as safe and as effective as its approved reference product.

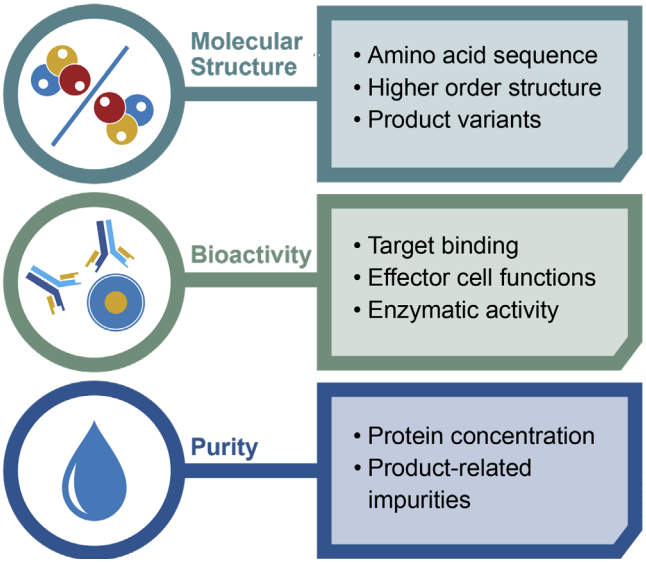

Figure 2: Examples of Attributes Measured for in the Comparative Analytical Assessment

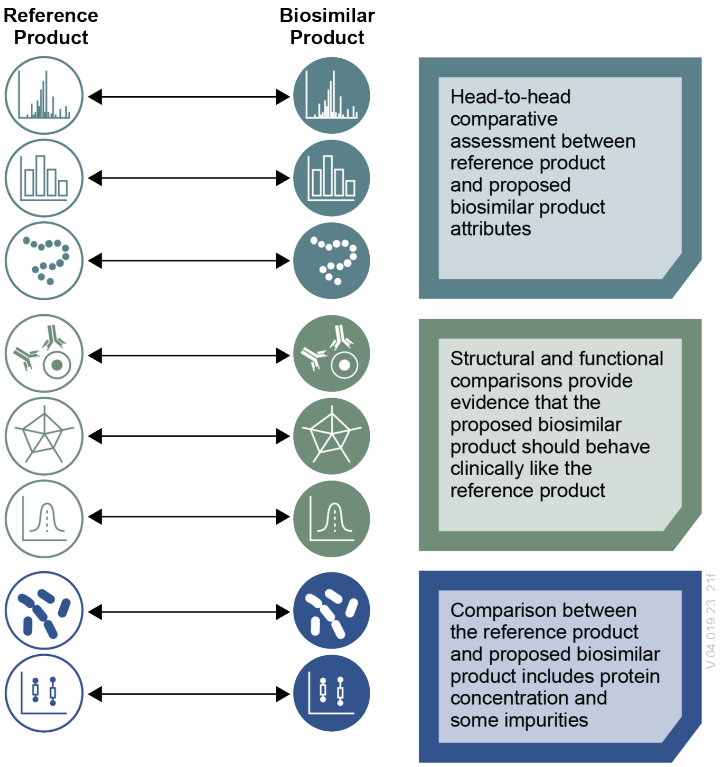

Figure 3: The Comparative Analytical Assessment Includes a Head-to-Head Comparison of the Proposed Biosimilar Product Against the Reference Product