# Discussion Questions

## Level 2: Regulatory and Scientific Concepts

This document provides knowledge assessment questions to support Level 2 learning materials, which explore more in-depth regulatory and scientific concepts related to biological products (also called biologics), including biosimilar products (also called biosimilars), and interchangeable biosimilars) than Level 1 materials. These questions are intended to aid in teaching biosimilar content by facilitating discussion and understanding of biosimilars among students enrolled in health care degree programs.

You may need to modify the questions or discussion responses to align with your specific health specialty or teaching needs. Refer to the FDA's website for additional information and other teaching resources on biosimilars.

## Knowledge Assessment Questions

### Why does the biosimilar approval process differ from the reference product's approval process?

The statutory approval pathway for biosimilars is different than the statutory approval pathway for reference products. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar and its reference product—not to independently establish the safety and effectiveness of the proposed biosimilar, as is expected for a reference product. This generally means that biosimilar developers do not need to conduct as many expensive and lengthy clinical trials.

**Note:** All FDA-approved biologics undergo a rigorous evaluation so that health care providers and patients can be assured of the safety, effectiveness, and quality of these products.

### How can we know that a biologic is safe and effective with its inherent variation?

Because biologics are generally made from living cells, there are inherent variations that can result from the manufacturing process. This is normal and expected for biologics, and lot-to-lot variation can be observed for reference products, biosimilars, and interchangeable biosimilars. FDA expects biologic manufacturers to have a strategy to control for the pattern and degree of variations between different lots to help ensure consistent safety and effectiveness. Manufacturers also demonstrate that biosimilars have the same type and pattern of variations as their respective reference products. For biosimilar approvals, FDA evaluates the totality of evidence, based on comparisons between the proposed biosimilar and the reference product, to support reliance on the FDA's determination that the reference product is safe and effective (**Figure 1**). Biosimilar manufacturers must demonstrate that the biosimilar is highly similar to and has no clinically meaningful differences from the reference product through comprehensive comparative analytical studies, clinical pharmacology studies, and additional clinical studies, as needed.

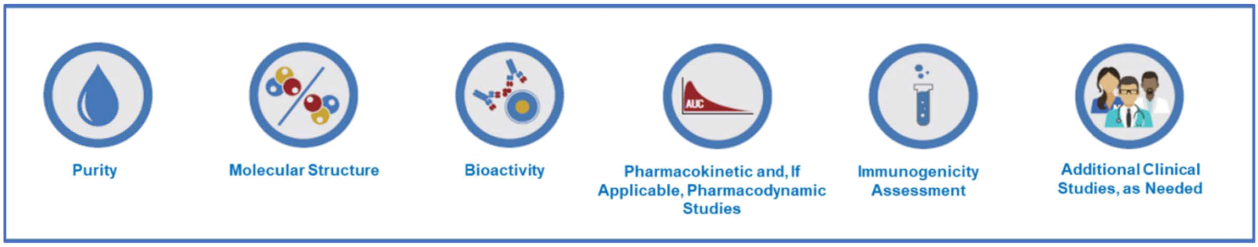


*Figure 1: Assessments Used to Compare a Biosimilar to Its Reference Product*

### What is the FDA's Totality of the Evidence approach to approving biosimilar and interchangeable products?

When the FDA makes a regulatory decision about whether a proposed product is "biosimilar" to its reference product, it doesn't look at just one piece of evidence or study to make its determination. The FDA examines data

generated from numerous scientific studies using state-of-the-art technologies to compare the structure, biological activity, and other molecular properties of the proposed biosimilar and its reference product. The FDA considers all of these data and information together to assess the extensive comparisons between analytical, pharmacologic, and additional clinical data, as needed, to demonstrate that a proposed product meets the standards for biosimilarity.

### What is the role of comparative clinical studies in the biosimilarity assessment?

Clinical studies that demonstrate pharmacokinetic (PK) similarity (i.e., similar exposure) can provide supporting evidence for a determination that there are no clinically meaningful differences in safety and efficacy between the proposed biosimilar and the reference product. Demonstrating pharmacodynamic (PD) similarity (with suitable PD biomarkers) can provide supporting evidence for similar efficacy, where applicable. Comparative immunogenicity assessments inform the incidence and severity of human immune responses between the proposed biosimilar and reference product. A comparative clinical study comparing safety and efficacy can provide supporting evidence for similar safety and efficacy.

### What is a comparative analytical assessment? What types of data are generated and analyzed?

The comparative analytical assessment includes the generation and analysis of data from a comprehensive and robust battery of comparative physicochemical and functional studies. These studies leverage state-of-the-art techniques to measure and compare multiple molecular properties (or "quality attributes" of the proposed biosimilar and its reference product. This assessment includes evaluation of attributes which may be associated with the biosimilar and reference product's bioactivity, pharmacokinetics (PK), pharmacodynamics (PD), safety, efficacy, and immunogenicity. The comparative analytical assessment is central to biosimilar development, since a product that is analytically highly similar to its reference product should behave like its reference product clinically in terms of safety and effectiveness.

### What are post-translational modifications, and why are they important when evaluating a biosimilar?

Post-translational modifications (PTMs) occur after the translation of mRNA into a protein. During the manufacturing process, proteins may undergo a number of PTMs, which are a natural consequence of their derivation from living cells. PTMs may impact protein folding and higher-level structure, therefore impacting its function and interactions, and may affect the elimination, distribution, or potential immunogenicity of therapeutic proteins, including biosimilars. PTMs are one common source of heterogeneity in biological products, and are carefully controlled. The comparative analytical assessment identifies and characterizes any differences between the biosimilar and reference product in post-translational modifications and other important molecular properties.

### What are interchangeable biosimilars?

A biosimilar approved as interchangeable means that it may be substituted for the reference product without intervention from the health care provider, subject to state laws (**Figure 2**). In addition to establishing biosimilarity, interchangeable biosimilar manufacturers generally conduct a switching study in which patients alternate between the reference product and the proposed interchangeable biosimilar multiple times over a specific period of time and are compared to patients who are just being treated with the reference product. The results must show no decrease in effectiveness or increase in risk associated with switching between the products.

**Note:** Laws addressing pharmacy-level substitution will vary from state to state. Pharmacists should contact their state board of pharmacy for the most up-to-date information.

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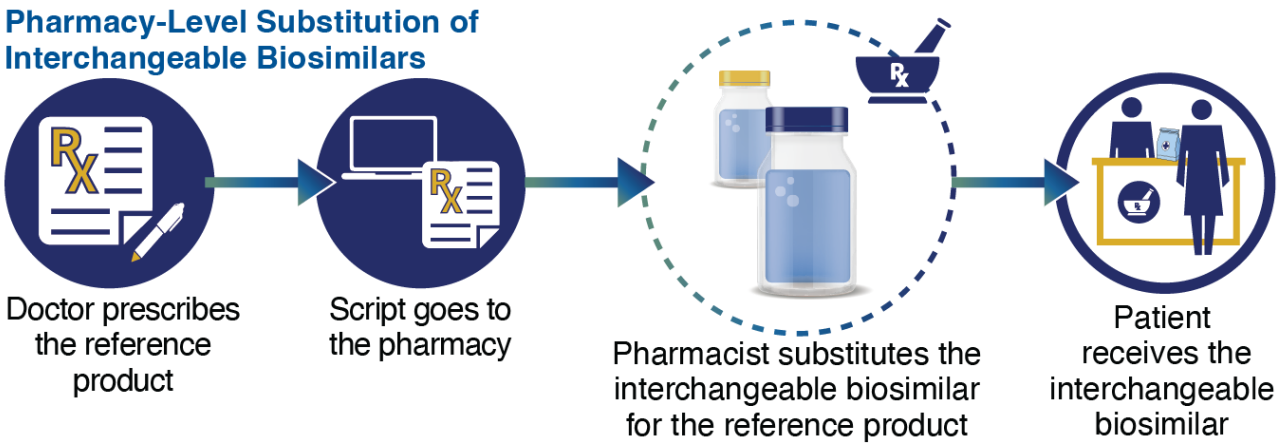


*Figure 2: Pharmacy-Level Substitution*

### Can pharmacists switch or substitute a biosimilar for its reference product?

Healthcare professionals can generally prescribe biosimilars and interchangeable biosimilars just as they would prescribe other medications. FDA-approved interchangeable biosimilars may be substituted for the reference product without the intervention of the prescribing health care provider, subject to state laws. Since many states have varying laws that address substitution of biological products at the pharmacy level, it is important for prescribers and pharmacists to understand the pharmacy practices in their state.

### How and why might a biosimilar label differ from the reference product label?

Biosimilar labeling generally incorporates relevant data and information from the reference product labeling, including clinical data that supported FDA's determination of safety and effectiveness for the reference product. As a general matter, biosimilar labeling should not include descriptions of or data from comparative clinical studies that support a demonstration of biosimilarity, as such studies are not designed to independently demonstrate safety and effectiveness and thus are not expected to facilitate an understanding of product safety and effectiveness. The text of the biosimilar labeling, however, does not have to be identical to the reference product. Biosimilar labeling will generally contain a "Biosimilarity Statement" that describes the product's relationship to its reference product. In addition, a biosimilar applicant may seek licensure for fewer than all of the conditions of use (e.g., indications, dosing regimens) approved for the reference product, so health care professionals should review the prescribing information for the biosimilar to determine the conditions of use for which the biosimilar is approved.

### What questions might a patient have about biosimilars, and how can providers respond to those questions?

Patients may have questions regarding: (1) the safety of the biosimilar; (2) the efficacy of the biosimilar; and (3) cost and affordability of the biosimilar. Discussions on the FDA's rigorous approval process of the biosimilar and information on the biosimilar's safety and effectiveness as compared to the reference product may help address many patient questions. Information about insurance coverage and cost may also help patients understand their treatment options. The FDA has also developed resources that address other common questions. For more information on patient education, please visit: https://www.fda.gov/drugs/biosimilars/patient-materials.