# Biosimilars Info Sheet

## Level 1: Foundational Concepts

## Manufacturing and Variation

Biological products (also called biologics) are generally large, complex molecules that range in size and complexity. Biologics include reference products, biosimilar products (also called biosimilars), and interchangeable biosimilar products (also called interchangeable biosimilars). Therapeutic proteins, such as monoclonal antibodies, are examples of biological products. Many therapeutic proteins are produced by recombinant DNA technology in animal or microbial cells (Figure 1). During the manufacturing process, these engineered cells make many copies of a therapeutic protein with the same amino acid sequence. Very small changes can occur to one or more amino acids in a given protein through a process called post-translational modification. For example, during protein production, cells may add sugar molecules onto specific amino acids of the protein in a process called glycosylation, which is a type of post-translational modification. A variety of sugars may be added to the protein molecules being produced. Therefore, although a single type of protein is being manufactured, the sugars that are added on make the individual protein molecules slightly different from each other. The resulting biologic ends up being a mix of these individual protein molecules with various sugars attached to them. This is true for reference products, biosimilars, and interchangeable biosimilars.

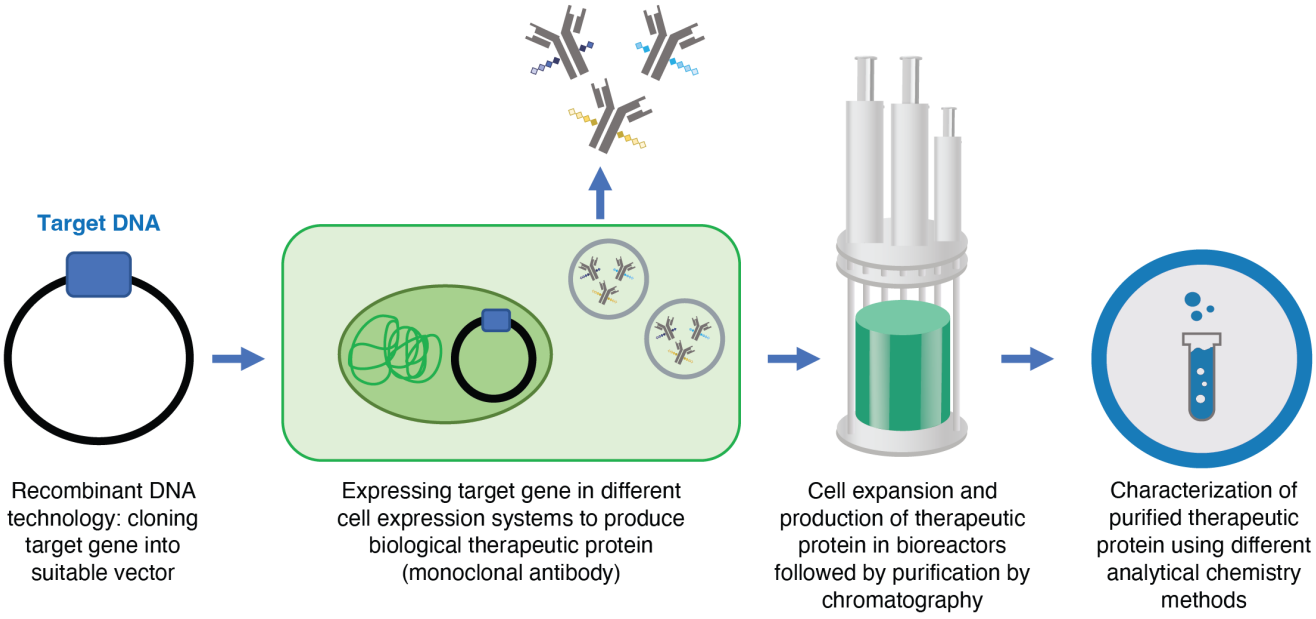


*Figure 1: Summary of Manufacturing Process of Reference Products and Biosimilar Products*

Small variations in biologics, whether they are reference products, biosimilars, or interchangeable biosimilars, can be expected within each lot and between lots. As an analogy, one can think of the individual protein molecules with their variety of post-translational modifications to be like jellybeans made from the same template but manufactured in a variety of colors Figure 2, top panel). The resulting biologic would be like a big jar of many different colored jellybeans, where each jar of jellybeans ends up with a slightly different mix of colors. When assessing biosimilarity, FDA requires studies that show that the biosimilar is highly similar to the reference product. Because of the variety of molecules that may be present in the reference product (illustrated as different jellybean colors), and because the mix is slightly different each time, a biosimilar is evaluated not just on an individual molecule (e.g., jellybean) level, but also on the pattern of variants (e.g., mix of colors) in the biosimilar and the reference product.

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.

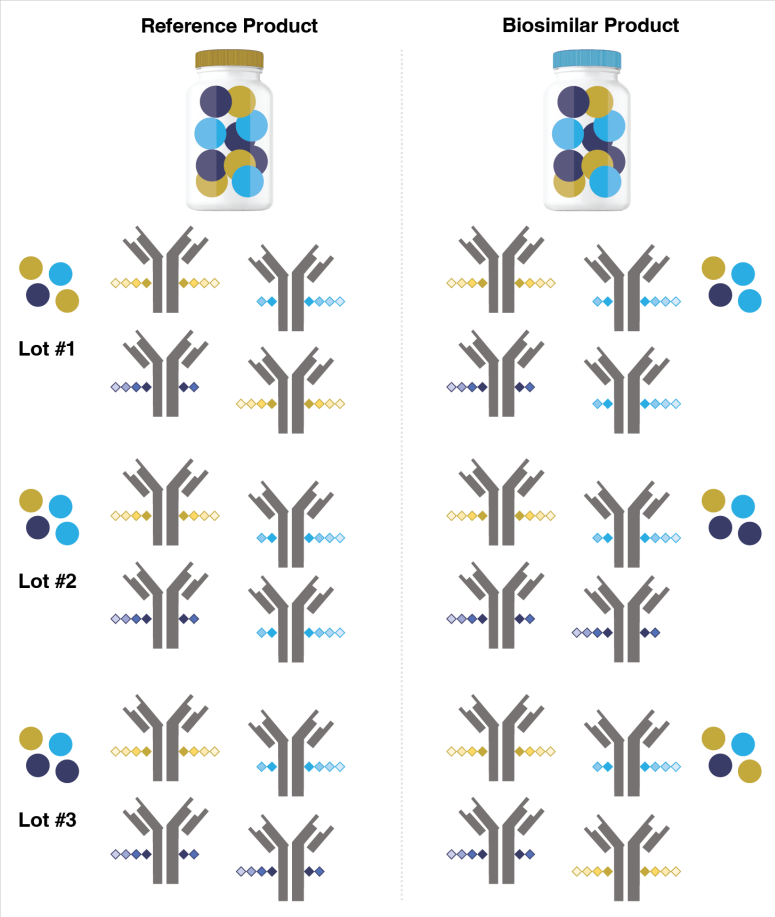


*Figure 2: Inherent Variation Is Observed in Both the Reference and Biosimilar Products During the Manufacturing Process as Shown by Different Colored Diamonds Representing Glycosylation*

### What Does It Mean to Be "Highly Similar"?

Slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process for biologics, regardless of whether the biologic is a reference product or a biosimilar. The manufacturing process for both reference products and biosimilars is carefully controlled and monitored to keep the variations within acceptable limits. State-of-the-art technology is used to compare the structure and function of the biosimilar to the reference product. The manufacturer of a biosimilar conducts these analytical comparisons side- by-side with the reference product to demonstrate that the biosimilar is highly similar to the reference product. Minor differences in clinically inactive components between the reference product and the proposed biosimilar are acceptable. For example, these could include minor differences in the stabilizer or buffer used in the biosimilar as compared to what is used in the reference product. Any analytical differences between the proposed biosimilar and the reference product are carefully evaluated by FDA to ensure the biosimilar is highly similar to the reference product and meets FDA's high approval standards.

### What Does It Mean to Have "No Clinically Meaningful Differences"?

A manufacturer must also demonstrate that its proposed biosimilar has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (i.e., safety and effectiveness). This may be demonstrated through human pharmacokinetic (i.e., exposure) and pharmacodynamic (i.e., response) studies, an assessment of clinical immunogenicity, and if needed, comparative clinical studies.