Biosimilars Info Sheet

Level 2: Regulatory and Scientific Concepts

Variation in Biological Products

The structure of biological products (also called biologics) is typically more complex than that of small molecule drugs. As a result, biologics are often more complicated to manufacture, process, and purify. They are typically manufactured from living organisms (e.g., microorganisms, animal cells) and therefore, inherently contain many slight variations within lots that are manufactured at different times (also called lot-lot variation). The inherent variation occurs naturally during the manufacturing process in reference products, biosimilar products (also called biosimilars), and interchangeable biosimilar products (also called interchangeable biosimilars).

For example, during the manufacturing of therapeutic proteins (shown as monoclonal antibodies in **Figure 1**), sources of variation include changes that occur as cells make proteins (called post-translational modifications). Post-translational attachment of biochemical groups has the potential to affect the function of the protein. Other post-translational modifications can be a consequence of manufacturing process operations (e.g., glycation resulting from incubation of a protein with reducing sugars) or certain storage conditions.

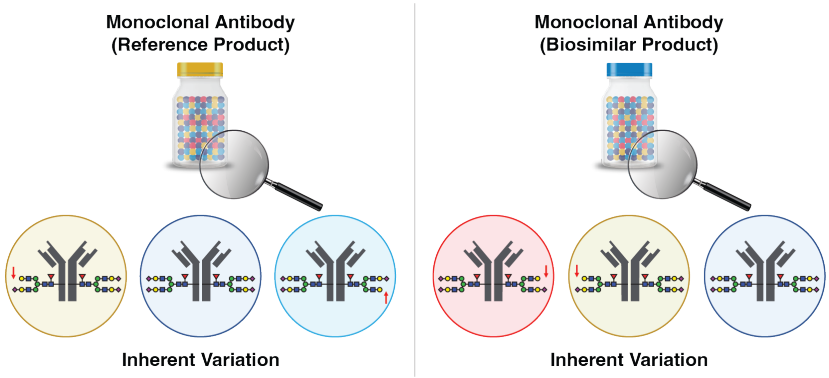

Figure 1: Inherent Variation Is Observed in Both Reference Products and Biosimilar Products, Shown Here as Monoclonal Antibodies, During the Manufacturing Process (as Indicated by Red Arrows Representing Small Differences in Glycosylation (Identical Biological Variants Are Depicted as Circles with the Same Color)

Examples of the types of variations that can occur specific to the structure of monoclonal antibodies are indicated by gray text boxes in **Figure 2**. These can include changes such as the formation of alternative disulfide pairings, deamidation and the formation of isoaspartyl residues, fragmentation of the linker region, cyclization of N-terminal glutamine residues to pyroglutamate, truncation of C-terminal lysines, and changes to the N-glycosylation chain (depicted with multicolored shapes in **Figure 2**). Therefore, both reference products and biosimilars can exhibit inherent variations within and between lots.

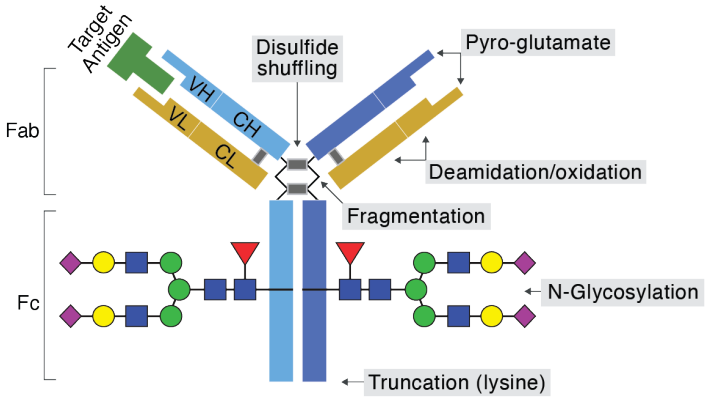

Figure 2: A Monoclonal Antibody Showing Examples of Different Types of Inherent Variation (as Indicated by the Gray Text Boxes and Solid Arrows)

Biosimilar manufacturers assess the distribution (or range) of variability between lots of the reference product and lots of the proposed biosimilar to ensure they are within an acceptable range. For approval, biosimilar manufacturers need to show that their products have similar patterns of variation compared to the reference product to support a demonstration of biosimilarity (i.e., the biosimilar is highly similar to the reference product).