BIOSIMILARS 101

What is a biologic medicine?

Biologics are medicines that are made by or from living cells though highly complex manufacturing processes and must be handled and administered under carefully monitored conditions. Biologics are used to prevent, treat, diagnose, or cure a variety of serious illnesses like cancer, chronic kidney diseases and autoimmune disorders, such as rheumatoid arthritis and inflammatory bowel disease. Biologic medicines are generally injected or infused into the patient. Because the active substance molecules are typically 200 to 1,000 times larger than chemically-synthesized, small molecule medicines, which typically come in tablet or capsule form, they are far more structurally complex and sensitive to changes in their environment. This sensitivity to manufacturing and handling therefore makes biologics more difficult to produce than chemically-synthesized small molecule medicines.

What are biosimilars and interchangeable biological products?

In 2010, the Biologics Price Competition and Innovation Act (BPCIA) established a regulatory pathway for two new types of biological products: biosimilars and interchangeable biological products. A biosimilar is exactly what the name implies — it is a biologic that is "similar" to another biologic drug already approved by the U.S. Food and Drug Administration (FDA). Under U.S. law, a biosimilar is approved based on a showing that it is "highly similar" to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. The FDA will only approve a biosimilar product if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product.

An interchangeable biological product is a product that is both biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. Interchangeable products are expected to produce the same clinical result in any given patient as the reference product, and must also demonstrate that there is no increased risk associated with alternating or switching between the interchangeable product and the reference product compared with using only the reference product. Because of these additional standards, an interchangeable biological product may be substituted for the reference product, subject to state pharmacy laws, by a pharmacist without the intervention of the health care provider who prescribed the reference product.[1]

Are biosimilars generic versions of biological products?

No. Generic drugs are **bioequivalent** copies of brand-name drugs. This means they have the same active ingredient, and are the same as the brand-name drug in dosage form, strength, route of administration, and conditions of use.[2] Biosimilars are highly similar to the reference product that they were compared to in terms of safety, purity, and potency, but have allowable minor differences in clinically inactive components because they are made from living organisms.

What is the status of the implementation of the Biologics Price Competition and Innovation Act (BPCIA) of 2009?

In 2010, Congress approved the BPCIA, which created an abbreviated approval pathway for biosimilars and provided 12 years of data protection for biologics. The legislative intent was to balance increased competition from biosimilar products with the need to provide biopharmaceutical researchers with certainty to make long-term research and development decisions and support future medical innovation. Since then, FDA has been working to issue guidance to resolve key scientific policy issues to implement the legislations.

PhRMA supported the enactment of the BPCIA and has actively participated in FDA's ongoing efforts to implement the statute. PhRMA's consideration of biosimilar policies is guided by our support for:

- **Science-based implementation** of the BPCIA and regulatory decision-making;
- **Patient safety** through effective identification of biologics and robust pharmacovigilance;
- **Healthcare provider and patient choice** in prescribing;
- **Regulatory transparency** that enables stakeholders to understand the basis for FDA's decisions; and
- **Long-term stability of the biosimilar user fee program** through financial transparency, efficiency, and accountability.

To date, the agency has issued several draft and final guidance documents to assist sponsors in generating data to support biosimilar applications. In addition, FDA guidance and regulations provide insight into the agency's current thinking regarding how it will evaluate and understand significant regulatory questions. Key guidances that remain on the CDER agenda include labeling for biosimilar biological products and considerations in demonstrating interchangeability to a reference product.

What are the elements of the abbreviated approval pathway for biosimilars?

BPCIA permits appropriate reliance on what is already known about a drug.[3] This approach enables sponsors to save time and resources in the development process by avoiding unnecessary duplication of human or animal testing. To achieve this, FDA has outlined a stepwise approach to generate data in support of a

1. FDA, Scientific Considerations in Demonstrating Biosimilarity to a Reference product, (2015), available at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

2. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/

demonstration of biosimilarity, including analytical, preclinical, and clinical data.

FDA determines the nature and scope of clinical studies after determining the extent of residual uncertainty about the biosimilarity of the two products after conducting extensive structural and functional characterization and, where relevant, animal studies. This approach, consistent with a longstanding Agency approach to evaluation of scientific evidence, is what FDA calls a "totality-of-the-evidence approach" in evaluating biosimilarity, with each step dependent upon the FDA's evaluation of residual uncertainty with regard to the similarity of the two products.[4]

What is extrapolation and how is it important for biosimilar development?

Biosimilars and interchangeable biological products can only be approved for indications of use that have been previously approved for the reference product. However, under the abbreviated pathway, the potential exists for a biosimilar or interchangeable biological product to be approved for one or more of the conditions of use for which the US-license reference product is labeled based upon extrapolation of data intended to demonstrate biosimilarity in one or more conditions of use. Consequently, two biosimilars of the same reference product may be approved on the basis of data for different indications.

In order to allow extrapolation of data, FDA requires sufficient scientific justification. FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation in accordance with guidance from FDA.[5]

Are there any unique safety considerations to be aware of with biologic products?

All biologic medicines have the potential to cause unwanted immune responses in the body that can cause serious health effects such as allergic reactions or anaphylactic shock, counteraction of drug effectiveness or, most seriously, blocking of both the drug and the endogenous protein; this is called immunogenicity. Recognizing the need to protect patient safety, Congress mandated FDA to require immunogenicity testing for biosimilars in the abbreviated pathway.

The practice of monitoring the effects of medicines after they have been approved for use by the FDA, especially to identify and evaluate serious adverse drug reactions, is called pharmacovigilance. Tools such as product names, accurate record-keeping, and physician and patient knowledge about potential adverse drug reactions are all essential for effective pharmacovigilance. For biologics, the potential for immunogenicity makes the accurate reporting and attribution of serious side effects to the correct biologic(s) critically important to detecting any safety signals between and amongst products.

Are there any special requirements for the manufacturing of biologics?

Due to the fact that biologics are manufactured in living cells, their function is highly sensitive to environmental changes. Even small changes to a biologic's (including biosimilars and interchangeable biologic products) manufacturing process, formulation or packaging can potentially affect the product's structural, functional and clinical properties. Because of this, any changes made during the manufacturing process are carefully regulated by FDA to ensure products remain safe and effective for patients.

In addition, sponsors of all biosimilar and interchangeable products must demonstrate to the FDA that the biological product is manufactured, processed, packed, or held in facilities that meet standards designed to assure that the biological product continues to be safe, pure, and potent.

3. FDA, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, (1998), available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

4. The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* provides insight into the concept of the *totality-of-the-evidence approach* in a different context (i.e., considerations of both the quantity and quality of the evidence to support effectiveness for drugs and biological products). Some of the principles discussed in that guidance may also be relevant in the design of a development program to support a demonstration of biosimilarity.

5. FDA, Scientific Considerations in Demonstrating Biosimilarity to a Reference product, Page21(2015), available at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf