Overview

Biosimilars
FORUM

Biosimilars FORUM

Partnership for Biosimilars Education and Access™

BIOSIMILARS OVERVIEW

ABOUT THE BIOSIMILARS FORUM

In 2015, the first biosimilar was approved in the U.S., and there are more than 50 biosimilars on the way. Their introduction may help expand access to high-quality treatment options for clinicians and patients as well as reduce costs to the health care system. Everyone involved—health care providers, payers, regulators, policymakers, patient advocates, and patients—needs a source of clear, unbiased, evidence-based information to better understand biosimilars and make wise decisions on policy and use.

The Biosimilars Forum was incorporated in Washington, DC, as a nonprofit organization to raise awareness on biosimilars and provide evidence-based biosimilars education and advocacy in the U.S. The founding members of the Biosimilars Forum represent the majority of companies with the most significant U.S. biosimilars development portfolios, including: Allergan, Amgen, Boehringer Ingelheim, Coherus BioSciences, EMD Serono, EPIRUS Biopharmaceuticals, Merck, Pfizer, Samsung Bioepis, Sandoz, and Teva.

The Biosimilars Forum launched the *Partnership for Biosimilars Education and Access* to provide an opportunity for stakeholders, health care professionals, patients, and companies developing biosimilars for the U.S. to work together to help shape the development of biosimilars, improve education, and expand treatment options and access to biological medicines.

This overview covers what biosimilars are, how they may be developed and manufactured, the regulatory procedures around approval and use, and how they will be used to expand treatment options for U.S. patients.

To learn more about biosimilars, the Forum, and how to get involved, visit BiosimilarsForum.org or go to @USBiosimilars to follow related conversations and join the dialogue.

Biosimilars Overview

The Foundation: What Are Biological Medicines?

Biological medicines, also known as biological therapies or "biologics," are medicines that are produced by living organisms, including human, animal, or microorganism cells. Proteins, antibodies, vaccines, gene therapies, and plasma treatments are examples of biologics. Biologics can either be extracted from natural organisms or produced via recombinant DNA technology (sometime referred to as "biotechnology").

Biologics are more complex than traditional, chemically synthesized small molecule medicines in a number of ways, including in their molecular size, three-dimensional structure, inherent variability, stability, and manufacturing processes. Although the first biologics were often manufactured by purifying them from animal tissues, since the 1980s many biologics are now produced through recombinant DNA technology, which allows living cells to manufacture proteins and other products of interest in an industrial setting. This has led to increased consistency, yield, and purity.

Biologics are more complex than traditional, chemically synthesized, small molecule medicines.

Biologics generally work within a patient's body by supplementing, interrupting, or directing natural processes and signals in order to treat a specific disease or disorder. Some of the most difficult-to-treat diseases, such as cancer, anemia, and autoimmune disorders (e.g., multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease) are best treated with biologics. Many biologics are delivered in a health care setting in the form of an injectable or in a solution to be administered intravenously, and some are self-administered at home. Most biological medicines must be stored at low temperatures.

Each new biologic that is approved by the U.S. Food and Drug Administration (FDA) may someday serve as the model, known as the reference product, for a biosimilar.

Core Principles of Biosimilars

What Is a Biosimilar?

Biosimilars are biological medicines that are approved based on a demonstration that they are highly similar to a previously approved biological medicine, known as a reference product. A biosimilar must be determined by the FDA:

1. to be highly similar to the reference product notwithstanding minor differences in clinically inactive components and
2. to have no clinically meaningful differences compared to the reference product in terms of safety, purity, and potency.

Some biosimilars may be nearly indistinguishable from their reference biologic, while others may justifiably exhibit some differences in structure or biologic function. Biosimilars are neither required nor expected to be identical to the reference biologic, which itself has inherent variability, but must be *highly similar with no clinically meaningful differences.*

The nature and extent of activities of biological medicines in the body are important. The "mechanism(s) of action," of a reference biological medicine (a detailed understanding of how the medicine works) must be understood in detail to clearly understand how the structure of the biologic is related to its function in the body and how changes in the structure of the biologic may affect its function. When the mechanisms are well understood, a biosimilar can be comprehensively developed alongside its reference product to confirm that it will work in the same way in patients. A biosimilar and its reference product should have the same mechanism(s) of action for the each of approved indications of use, but only to the extent these are known. Biosimilars must meet the same product and manufacturing quality standards as any FDA-licensed biologic medicine.

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The manufacture of biologics is complex and must be precisely controlled to obtain consistent results. Companies that manufacture biologics need to have state-of-the-art tools and techniques to manage sensitivity in cell culture, protein purification, product fill, and packaging. Because they are made in living

organisms, all biologics (both reference products and their biosimilars) can vary slightly from lot to lot and more noticeably throughout the lifecycle of the medicine as changes to manufacturing are made.

When changes are made in the manufacturing process of a biologic, the manufacturer must check whether or not these changes are clinically relevant. Further, all such proposed changes are carefully examined by health authorities, including the FDA. Both lot-to-lot variability and manufacturing changes are closely evaluated, regulated, and monitored by the manufacturer and the FDA.

The first U.S. biosimilar was approved in 2015, and multiple other biosimilars are under review at the FDA. Biosimilars have been available and used safely in Europe since 2006. In addition, biosimilars have been approved in other well-regulated regions or countries, including Australia, Canada, Japan, and Korea, thus expanding treatment options and access for health care professionals and patients.

Totality of Evidence

A biosimilar is approved by the FDA based on the "totality of evidence" – extensive analysis (of structural features and measurements of how well the medicine works), as well as animal and human clinical comparisons that confirm that the biosimilar is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and establishing that there are no clinically meaningful differences between the biosimilar and the reference product in terms of the safety, purity, and potency of the product.

In biosimilar development, the foundation of knowledge about the biosimilar begins with the collection and analysis of available public information and experience with the reference product. This includes published scientific studies on the mechanism(s) of action, the structural and functional aspects of the reference product, as well as peer-reviewed clinical trial and observational data. Published clinical trial and observational data for the reference product can be important to the design of comparative clinical studies where appropriate. In addition, a biosimilar sponsor will legally purchase the reference product over time in order to study the properties of the drug substance (active ingredients) and the drug product (formulation). This publically available information and hands-on testing of purchased material often enables biosimilar sponsors to understand the relationship between the structure of the molecule and how

it functions, which together with an understanding of the mechanism of action, enables the design and development of the biosimilar.

Robust analytical and pharmacological data comparing a biosimilar candidate to the reference product is a critical component in establishing the totality of evidence necessary for regulatory approval of a biosimilar. Modern analytical testing and pharmacology assays are extremely sensitive and are generally more capable of detecting a structural or functional difference between a biosimilar and reference product than are human clinical studies.

As part of this totality of evidence approach, a more comprehensive analytical comparison of the biosimilar and the reference product has the potential to reduce the amount of clinical data that are needed to address residual doubt.

> *Health care providers and their patients can be assured that a biosimilar will work just as safely and effectively as its reference product.*

Studies conducted in humans to support biosimilar approval should directly compare the biosimilar to the reference product in a population that is sensitive to detect any potential difference between the products. Generally the appropriate clinical trial population should be uniform, should have a high treatment effect, and where possible, avoid other medications given at the same time that could complicate analysis. These studies are intended to confirm that the biosimilar works the same in humans as the reference product and to assess immunogenicity, or the comparative human immune response to the biosimilar and reference product. Comparative immunogenicity testing of a biosimilar and reference product should be conducted in healthy volunteers or patients who have functional immune systems to ensure that a difference can be detected should one exist.

These clinical studies are not designed to establish the benefit and risk profiles of either the biosimilar or reference product. Instead, they are intended to reduce any residual uncertainty that may exist from the prior comparative analytical and animal studies in determining that the biosimilar is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and to validate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

When the comparative analytical, animal, human clinical, and immunogenicity data obtained with the biosimilar are added to the knowledge from publically available information and experience with the reference product, health care providers and their patients can be assured that a biosimilar will work just as safely and effectively as its reference product.

Stepwise Approach

When developing a biosimilar, a "stepwise" approach is followed in establishing the totality of evidence to demonstrate that the biosimilar is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and to validate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

The stepwise approach begins with comparative analytical testing that is conducted to demonstrate physical, chemical, and functional similarity to the reference biologic. This includes detailed physicochemical study of the structure of the molecule, functional activities that include receptor binding to measure how well the biosimilar works, and immunochemical properties; an assessment of impurities that may be present; testing of the finished drug product; and stability of both the biosimilar molecule and the finished medicine product.

The *analytical testing* is followed by studies in animals to evaluate comparative pharmacology of the biosimilar and reference product. Importantly, these non-clinical studies will not only compare the biosimilar and reference product function and activity, but can also evaluate the impact of any analytical differences that may have been observed in the prior step.

The next step is to conduct comparative pharmacokinetic (PK) and pharmacodynamic (PD) or *"PK/PD"*studies in humans. These studies are often conducted in healthy individuals. A PK study measures what happens to the medicine when it is in the body, including the absorption, concentration, and clearance of the medicine from the body. A PD study evaluates what happens in the body in response to the medicine by testing the effect of a medicine on a physiological function through use of a "marker," or measurable attribute of activity or function. Comparative PK/PD studies can be conducted in healthy volunteers or patients, and are another level of evidence that helps prove that the biosimilar and reference products are highly similar and that there are no

clinically relevant differences in safety and efficacy between the biosimilar as compared to the reference product. Just as in prior steps, comparative PK/PD studies can also be designed so that they help inform the relevance or irrelevance of any differences observed either in structure or function as measured by the prior analytical and animal studies.

The PK/PD studies may then be followed by *confirmatory clinical studies* that are conducted in patients with the disease being treated. When necessary, clinical studies to support biosimilar approval directly compare the biosimilar to the reference product in a patient population that is sensitive to detect any potential difference between the products. In general, the appropriate clinical trial population should be uniform, should exhibit high treatment effect, and where possible, avoid other medications given at the same time that could complicate analysis. These studies are intended to confirm that the biosimilar works the same in humans as the reference product and to assess immunogenicity, or the comparative human immune response to the biosimilar and reference product.

Comparative immunogenicity testing of a biosimilar and reference product should be conducted in healthy volunteers or patients who have functional immune systems to ensure that a difference can be detected should one exist.

These clinical studies are not designed to establish the benefit and risk profiles of either the biosimilar or reference product, but instead to reduce any residual uncertainty in determining that the biosimilar is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

The FDA has the discretion to determine that one or more of the above elements is unnecessary and encourages sponsors to discuss the relevance and extent of each of the elements based on the data obtained from the previous step.

Critical Quality Attributes

Based on the many years of study of the reference product, along with comprehensive public information, biosimilar manufacturers build an understanding of which structural aspects of the reference product can have an impact on clinical safety and

effectiveness. The most important of these structural attributes are known as “Critical Quality Attributes.” Biosimilar manufacturers use this knowledge to develop a hierarchy of importance of the many features of the molecular structure and manufacturing process that can be measured.

Numerous sophisticated analytical tests can enable biosimilar manufacturers to carefully measure and compare the structure and biological function of the reference product and biosimilar and to detect foreign or unwanted material from the manufacturing process. However, not all of the items that can be studied and measured are equally important.

The criticality of the quality attributes can be categorized as very high through very low based on their impact on safety and efficacy. For those that are very high, the biosimilar must match the observed range of the reference product. Statistical analyses are often conducted on important quality attributes to ensure that the assessment of equivalence is rigorous and impartial.

Comparison of quality attributes that are low or very low in criticality can be done without detailed statistical analyses. Differences between the biosimilar and reference product in these features are permissible, with the caveat that the differences are clearly known not to be clinically important.

Biosimilarity

Biosimilarity is established when the totality of evidence supporting a biosimilar is assembled through analysis of all public information, testing of the reference product, and the “stepwise” comparative development of the biosimilar and reference product.

Once satisfied that the assembled evidence is both adequate and sensitive to detect any potential differences, FDA will approve the biosimilar for use in one or more indications of use on the basis of the biosimilar being highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

Extrapolation

A biosimilar may be approved for one or more conditions of use (known as "indications and usage") for which its reference biological product is licensed but for which there was no head-to-head clinical comparison. This approval is based on the *extrapolation* of the totality of data obtained with the biosimilar in direct comparison to the reference product.

Extrapolation is the approval of a biosimilar for use in an indication held by the reference product, not directly studied in a comparative clinical trial with the biosimilar. Extrapolation is critical for the successful development of biosimilars and their potential benefit to patient access. The concept of extrapolation is an established and common principle of comparability used in pharmaceutical development for all biologic medicines.

The stepwise development of a biosimilar establishes that it is highly similar to the reference product in comparative analytical, animal, pharmacological, and if appropriate, clinical studies designed to be sensitive to clinically meaningful differences. Where scientifically justified, the totality of evidence along with the knowledge of the mechanism of action can be used to seek extrapolation to other indications.

The FDA examines requests for extrapolation on a case-by-case and indication-by-indication basis. Every indication for which extrapolation is sought must be scientifically justified. Approval of an additional indication through scientifically valid extrapolation expedites the development of biosimilars and eliminates unnecessary clinical studies, thereby increasing patient access to important therapies.

Extrapolation is critical for the successful development of biosimilars and their potential benefit to patient access.

Scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism of action(s) in each condition of use for which licensure is sought
- Pharmacokinetics (what happens to the medicine in the body) and pharmacodymanic (what happens in the body in response to the medicine) measures may also provide important information
- The immunogenicity of the biosimilar in different patient populations

- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to activities not related to treatment of the disease or condition)
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the *totality of the evidence* supporting biosimilarity.

Interchangeability

An interchangeable biologic is a biosimilar that produces the same clinical result as its reference product in any given patient. An interchangeable biosimilar can be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. The U.S. is the only country to have a separate "interchangeable" designation for biologics. The requirements for being designated as "interchangeable" in the U.S. are separate and additional to being designated as "biosimilar" and will be clarified by the FDA.

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An interchangeable biological product, in addition to meeting the biosimilarity standard, is expected to produce the same clinical result as its reference product in any given patient. It also must be demonstrated for a product used more than once that the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar and its reference product is not greater than the risk of using the reference product without alternating or switching. In essence, an individual experiences the same level of safety and effectiveness using the interchangeable biologic or its reference product regardless of alternation or multiple switching.

After a product is approved as either a biosimilar or an interchangeable biologic, the FDA will publish this information in an online database called the Purple Book. The Purple Book is updated when the FDA licenses a biological product under section 351(a) or section 351(k) of the Public Health Service Act (PHSA) and/or makes a determination regarding the date of first licensure for a biological product licensed under

section 351(a) of the PHSA. Health care professionals can check the Purple Book to see if a product is a biosimilar or an interchangeable biologic in a manner similar to the way that the Orange Book is used to check if FDA has found a generic drug to be therapeutically equivalent to its reference product.

While the FDA will designate biologic interchangeability, U.S. states regulate the practice of pharmacy, including laws describing how and when a pharmacist can substitute one drug for another. Initial state substitution laws were written based on generic drugs. The laws in each state must be updated to permit pharmacy substitution of an interchangeable biologic for a reference product and vice versa. Many states have either passed or are considering the needed legislation.

Key Tenets of the U.S. Biosimilars Regulatory Pathway

In the U.S., the regulatory pathway for all medicines, including biosimilars, is rigorous. At the core of the biosimilars regulatory pathway is the mandate that biosimilar sponsors must demonstrate that the biosimilar is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

The FDA regulatory pathway accounts for safety and efficacy for biosimilars in an analogous manner to the European Union, where biosimilars have been approved for use since 2006. As of the end of 2015, Europe had approved 12 different biosimilar products, which are now marketed under 18 different brand names. As a result, in Europe, clinicians and patients have benefited from the safe use of millions of doses of biosimilar medicines. Throughout this time, there have been no additional unexpected safety concerns about biosimilars that were not already known from the reference product.

The U.S. Regulatory Pathway for Biosimilars

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Patient Protection and Affordable Care Act (ACA) in 2010. The ACA was enacted to increase the quality and affordability of health care while reducing costs for individuals and the government. As part of this, an abbreviated licensure pathway was

created for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.

Definition of Biosimilar

According to the FDA, a biosimilar is a biological product that has been proven to be highly similar to a reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.

Definition of Interchangeable

When a biosimilar is determined to be interchangeable with its reference product, it can be expected to produce the same clinical result as the reference product in any given patient. It also must be demonstrated that for a product used more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the interchangeable product and its reference product is not greater than the risk of using the reference product without alternating or switching.

The designation "interchangeable" or "interchangeability," in reference to a biological product that is shown to meet the standards described in the Public Health Service Act, means that the biological product may be substituted by a pharmacist for the reference product without the intervention of the health care provider who prescribed the reference product, subject to state substitution laws.

351(k) Application Pathway Requirements

By definition, manufacturers of biosimilars in the U.S. seek FDA regulatory approval through a Public Health Service Act Section 351(k) application. The application must include information demonstrating that:

- The biological product is biosimilar to a reference product
- It utilizes the same mechanism(s) of action for the proposed condition(s) of use (to the extent the mechanism[s] are known for the reference product)
- Condition(s) of use proposed in labeling have been previously approved for the reference product
- Route of administration, dosage form, and strength is the same as the reference product

- The facility in which the biosimilar is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent

The data demonstrating biosimilarity must be derived from:

- Analytical studies demonstrating that the biological product is “highly similar” to the reference product, notwithstanding minor differences in clinically inactive components
- Animal studies, including the assessment of toxicity
- A clinical study or studies, including the assessment of immunogenicity and pharmacokinetic/pharmcodynamic studies that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product

Data demonstrating interchangeability must demonstrate that:

- The product is biosimilar to the reference product
- Can be expected to produce the same clinical result as the reference product in any given patient
- For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and its reference product is not greater than the risk of using the reference product without alternating or switching.

In the application process, the FDA may determine, at its discretion, that an element in the application process described above is unnecessary in the 351(k) application.

Biosimilars Approvals

Following submission of the complete 351(k) application, the FDA confirms that the product is indeed biosimilar to or interchangeable with the reference product. The facility where the biosimilar is manufactured must comply with the appropriate FDA inspections. At this time, the product is then officially licensed by the FDA for its designated therapy.

Sometimes manufacturers will submit a 351(k) application where some data were generated using a comparator product purchased outside of the U.S. While this is permissible in some defined circumstances, the FDA carefully reviews the data provided by the sponsor to demonstrate that the material purchased outside of the U.S. is fully comparable to equivalent U.S.-approved material. The reference product will always be the single biological product licensed previously as a new biologic (using Section 351(a) of the Public Health Service Act) against which a biosimilar is evaluated in an application submitted under Section 351(k).

Societal Benefits of Biosimilars

Some of the most difficult diseases that afflict people in the U.S., such as cancer, anemia, inflammatory bowel disease, and autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, psoriasis, and Crohn's and other inflammatory bowel diseases, are best treated with biologics. Many biologic treatments are delivered in a health care setting in the form of solutions to be injected or administered intravenously. While biologics make up a small percentage of the total number of drugs on the market, they still pose a significant health care cost, representing 23 percent of 2014 global pharmaceutical expenditures (which are in turn 9.3 percent of total U.S. health care spending). Since their origins in the 1980s, biologics have grown to be a $179 billion market in 2014 (EvaluatePharma. World Preview 2015, Outlook to 2020. 8th Edition – June 2015). This impact is predicted to grow because many new drugs under development are biologics.

The introduction of biosimilars is anticipated to help drive lower costs burdens for the U.S. health care system and help expand earlier, more consistent access to biological medicines. The RAND Corporation has projected that the introduction of biosimilar medicines in the U.S. will reduce direct spending on biologics by $44.2 billion from 2014 to 2024. Several biological medicines will go off patent by 2020, creating an opportunity to develop biosimilars from these reference products.

Benefits for Providers

The growth of the biosimilars market may provide expanded or earlier patient access to these important treatment options. These therapies have the potential to reduce financial and administrative barriers for patients although this has not yet been demonstrated given that only one biosimilar is currently available in the U.S.

Benefits for Patients

Biosimilars may offer a number of benefits for patients, including expanded insurance coverage within a class of treatments (FTC Report, June 2009) if both the reference product and biosimilar are available in a given formulary or if used in first-line therapy as permitted by the product label. This means that biologics use may increase, either as a result of earlier treatment initiation where medically appropriate or increased medication compliance. In the long term, expanded access to biologic medicines may lead to improved patient outcomes that will in turn provide significant savings to the U.S. health care system.

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Benefits for Payers and Systems

Biosimilars have the potential to generate savings and efficiencies for health care systems, which can help expand access to biologic medicines or free up resources for other important aspects of health care, including the development and use of new medicines.

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