



Biologics Biosimilars

- **Questions**
- **Policy**
- **Safety**

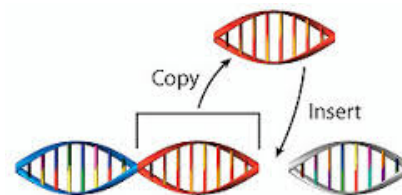
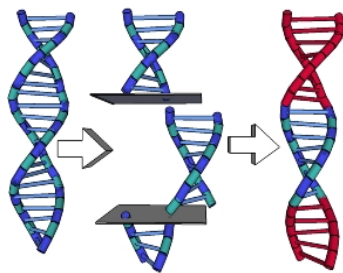
What are biosimilars?

Biosimilars are sometimes incorrectly and inappropriately called “generic” versions of original biological medicines. But unlike generic drugs, which are identical copies of medicines, biosimilars are not identical to the original biological medicines. Biosimilars are just that – similar but not identical. They too have been derived from living cell lines but both the cell lines and the processing methods can be different from the original biologic. Therefore, the biosimilars are similar but not identical to the approved branded product.

Biosimilars, when they become available in the U.S., will require evaluation and approval by the U.S. Food and Drug Administration (FDA) on the basis of analytical and clinical comparison to the already marketed product. The guidelines set by FDA for the approval of a biosimilar should be as rigorous and accountable as those for the original biologic in order to assure the same level of safety and effectiveness. FDA has yet to finalize guidance on the standards that biosimilars will have to meet.

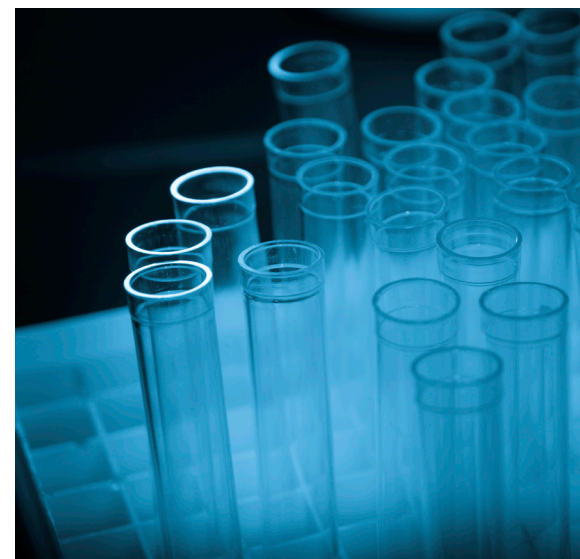
How are biologic drugs made?

Biologic drugs are much more complicated to produce than chemical drugs which are made from chemicals and are referred to as small molecules. Biologics are made from genetically identical copies of a master cell which has been changed through a technique called gene splicing. Gene splicing is a process for inserting materials from two or more genes into another gene to produce a unique protein or substance that will help the body combat an illness. The method for their production involves using this unique master cell to established cell lines which can then mass produce proteins and antibodies. These proteins and antibodies then work within a patient’s body to combat the disease or condition afflicting them.

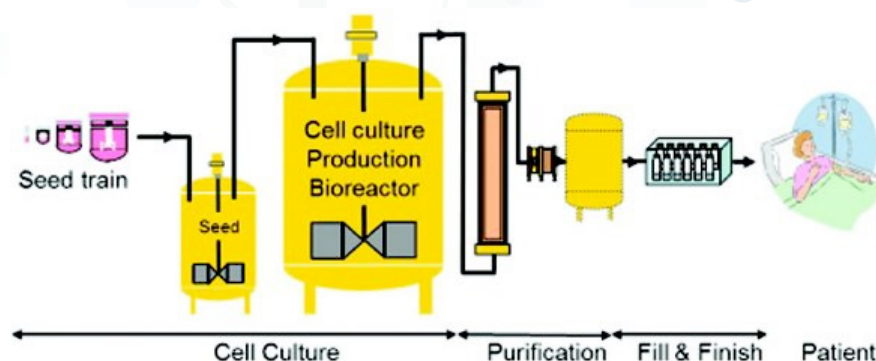


Gene Splicing

To produce these proteins the master cell is placed into a culture where it multiplies and then is transferred to large vats where the growing cells are processed and monitored at exacting conditions until the desired quantity of protein has been produced. This process results in the production of the specific protein needed for the biologic medication. The protein is then extracted from the cellular culture, purified, and stabilized. Thus each manufacturer of biologics has a cell bank to produce its own unique “cell line” derived from the master cell and using its own exclusive manufacturing process to produce its brand name biologic.



Biologic medicines must be processed using exact ingredients and conditions to achieve the desired outcomes. Even slight changes in the starting materials and/or the process may lead to very different results. In addition the outcomes may still vary “batch to batch.” Therefore, testing is very important to ensure that the product meets quality standards.



How do biologic drugs work in autoimmune diseases?

Unlike chemically based drugs that generally treat symptoms of disease (for example, aspirin for pain), biologic drugs target the underlying cause. For example, some biologics are antibodies that target very specific disease-causing cells, such as those causing rheumatoid arthritis, Crohn’s disease, psoriasis, and ankylosing spondylitis. In autoimmune diseases, the biologic medicine targets a specific immune cell which causes inflammation and results in damages to the joint, gut, skin, or organ involved in the disease process. Biologics are effective in the treatment of a number of autoimmune diseases and are often prescribed by physicians off label for autoimmune diseases for which they have not yet been approved for marketing by FDA.

Insulin, a very familiar biologic, has been used for many years for diabetic patients who can no longer make insulin on their own. Intravenous gamma globulin is another commonly known biologic that is made from human plasma and replaces proteins that are low or are missing in the patient’s blood.

Because biologics are targeted to work in highly specific ways, they not only potentially offer increased effectiveness against the targeted disease but also may lead to fewer side effects than are encountered in some other treatments. Biologic drugs such as monoclonal antibodies regulate the function of specific, defective cells that cause cancer growth without interfering with normal cells. For example, in cancer, biologics work by targetinactively dividing cells; but chemotherapy, because its action is “nonspecific,” often interferes with normally dividing cells as well as cancerous ones.

Are there safety issues with biologics?

Small differences between biologic products can have implications for individual patients. Autoimmune diseases are caused by an individual’s immune system attacking one’s own cells, organs and tissues. Since autoimmune patients have a heightened immune response, they may be affected by the immunogenicity (the ability of a substance to cause an immune response) of a biologic medicine. Because biologic drugs are larger and more complex than chemical small molecule drugs, they are also more likely to be recognized by the body as “foreign” and cause an “immune reaction.” Often, these reactions are mild and will subside over time, but it is something that providers and patients should know about and monitor.

Since proteins are digested, most biologics cannot be taken orally. Therefore, biologic drugs typically are injected into a vein or infused under the skin. Patients frequently experience some reactions, such as redness, swelling or soreness, at the site of injection. These may vary in severity and frequency. Moreover, because some biologics can lower the normal immune responses to infection and cancer cell detection, they have a small risk of increasing the chance of cancer and overwhelming infection.

Additionally, a very rare but serious reaction may also occur through the production of “neutralizing” antibodies. This occurs when the body produces antibodies that destroy not only the biologic drug but also any

amounts of the naturally produced protein that the drug replicates. This can be a life-threatening situation since the body does not have access to any form of this protein. Therefore, the prescribing physician (usually a specialist) closely follows the patient and weighs the benefit/risk ratio and the severity of disease when determining the best options for the patient. Pharmacovigilance (regularly monitoring all side effects of medication over time) is important for patient safety.

Are biologics as safe as chemical drugs?

All drugs sold in the USA must be approved by the FDA, a regulatory agency which uses strict tests of safety, efficacy, and quality. In addition, the manufacturing facilities for biologics are inspected to ensure that they meet quality standards. Biologics also are inspected by FDA on a “lot by lot” basis to ensure that each batch conforms to standards of purity and potency.

Why might a patient be prescribed a biologic?

Biologics have changed the way many very serious diseases are treated. In each disease category for which biologics are used, the goal may be different, such as destroying or halting the production of a cancer cell, replacing a missing protein or hormone, or targeting and suppressing the production of proteins causing damage. The patient’s physician assesses the seriousness of the condition and determines the goal of therapy. Often, in the case of autoimmune diseases, the choice is to start with less aggressive treatment and then progress, as needed and appropriate, to therapies with higher risk to achieve better control of the damaging effect of the disease.

Studies have shown that treatment with biologics can stop or slow the progression of the disease; and, in such a case, they may be used early-on in the course of disease progression to prevent irreversible damage to joints or organs. The decision to take a biologic or a traditional chemical drug is an individualized one based on the disease status and the patient profile.

Because biologics are highly specific therapies, they tend to work best for patients with the disease profile which the drug targets. In some cases, physicians may prescribe a “step therapy” whereby patients are started on a chemical drug and then moved to a biologic drug when the chemical drug is either not tolerated or no longer effective.

What about safety?

All biologic drugs are reviewed for safety and efficacy by the country’s regulatory agency before they are approved for use in humans. The FDA approves biosimilars in the United States. Patients who are prescribed a biologic drug are advised about and monitored for side effects. All severe adverse reactions should be reported to the manufacturer and the FDA (by the patient and the physician). These must be analyzed and reported by the manufacturer. In some cases, patients may be treated for side effects and remain on the biologic drug; in some other cases, the reactions may be serious enough to discontinue treatment, either temporarily or permanently. In all cases, the decision should be made by the physician in consultation with the patient based on the risks, benefits and alternatives.



How is the decision made about which biologic is best?

There are now many diseases with multiple biologic drug options. These include diabetes, cancer, autoimmune disease, hepatitis B and C, and anemia. In most cases, the biologic drugs each target different disease sites or different steps in causation or progression. The aim is to match the characteristics of the drug to the patient's profile, including genetic characteristics, disease site, status, and previous therapeutic response.

Physicians may adopt a “trial and error” approach through monitoring outcomes and side effects to determine the best biologic. Sometimes, a stepwise approach is best, whereby the patient is started on the biologic with lowest potency and/or adverse effects. If this does not work, the patient can be placed on a higher dosage or changed to a different drug.

The decision should consider also the impact of therapy on the patient. What are the time and support requirements for each drug? What are potential side effects, and what resources does the patient have to manage these?

What are the safety implications for biosimilars?

It is important to provide access to biologics including biosimilars to patients who need them. FDA should require that manufacturers of biologics and biosimilars conduct rigorous clinical testing to prove that the product works safely and effectively in each and every condition for which the manufacturer is seeking approval. Steps should be taken to assure appropriate tracking of adverse events for biologics and biosimilars so that any such issues are promptly and accurately identified.

What are some of the policy issues related to the approval of biosimilars in the United States?

There are a number of policy issues related to the approval of biosimilars that, as of this writing, remain open and/or are under consideration by the FDA. These policies will be crucial to protecting patient safety in connection with biosimilars.

- **Naming.** An important policy issue relating to biologics, including biosimilars, relates to how they will be named. There has been much debate over this issue in both the United States and in Europe. Europe requires that biological products, including biosimilars, be identified by brand name instead of by their “International Nonproprietary Name” (or “INN”). An INN is a globally recognized generic name for a biological, pharmaceutical, and other similar products. The biosimilars naming debate centers on whether these products must have distinguishable nonproprietary names as compared to their reference products. Some stakeholders have taken a position supporting shared nonproprietary names for biosimilars and their reference products, while other stakeholders urge that all biological products, including biosimilars, must have distinguishable nonproprietary names.

Stakeholders supporting distinguishable names have focused on the complexity of biologics and the diseases that these medicines treat. Many physicians, patient advocates, and other stakeholders believe that distinguishable names are important in order to ensure transparency and protect patients' safety. For example, distinguishable names can help to avoid confusion about which product is being prescribed, and can help to ensure that patients, physicians, and pharmacists understand the distinctions between products' characteristics and approved uses. Distinguishable names also facilitate, on a product-specific basis, accurate tracking of clinical outcomes and adverse events.

- **Defining “Similarity” and “Interchangeability” Standards.** In creating a pathway for approvals of biosimilars in the United States, the Affordable Care Act (ACA) established certain standards for “biosimilarity” and “interchangeability,” which FDA must take into account as it implements the biosimilars approval pathway. FDA's interpretation and application of the standards for “biosimilarity”

and “interchangeability” represent another policy issue related to approval of biosimilars in the U.S. For example, in order to approve a product as a “biosimilar” FDA must determine, among other things, that there are “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” In addition, under the ACA, a product that FDA deems to be “interchangeable” with the reference product is permitted to be substituted for the reference product without the intervention of the prescribing physician. (Note that some state laws may impose different standards for when an “interchangeable” biologic may be substituted for the reference product.) The Biologics Price Competition and Innovation Act (BPCIA) requires that the biosimilar is “highly similar” to an already approved biological product. Thus, FDA’s decisions about biosimilarity and interchangeability will have a significant impact on which medicines are approved, as well as how those medicines are prescribed by physicians, covered by health plans, and ultimately impact patient choice of the medicines.

- **Indication Extrapolation.** When the FDA approves a medicine for marketing in the United States, the FDA specifies one or more specific indications, or uses, for which the product is approved. Biologic therapies require FDA approval for each individual use that is included on their label. Another crucial policy issue related to the approval of biosimilars in the United States is whether or to what extent biosimilars may seek approval for an indication through “extrapolation.” Indication extrapolation describes a process in which a regulatory body would apply a biosimilar’s approval for one medical use to an *additional use* that mirrors another of the reference product’s approved indications. Extrapolation, if granted, would effectively provide a “shortcut” for a biosimilar to be approved for additional indications for which the reference product is approved. Regulators still would require a showing of therapeutic similarity for the product’s use in a particular population or for a particular disease, but less rigorous testing and data would be required as compared to the process of seeking approval for a specific indication in the first instance. On one hand, extrapolation potentially could reduce the costs of developing new indications and approved uses for biosimilar biological products. On the other hand, given the complexities of these medicines and the differences between biosimilars and their reference products, any potential benefits of extrapolation should be balanced against patient safety considerations and the need to ensure that sufficient testing is conducted prior to approvals of new indications for biosimilar biological products.
- **Notification and Substitution.** Once biosimilar medicines are approved, another key policy issue concerns whether, and under what circumstances, a “biosimilar” or “interchangeable” product could be substituted in place of the doctor’s prescribed medicine, and whether a pharmacist must notify a patient or the prescribing physician of that substitution prior to making it. As noted, federal law permits substitution for an “interchangeable” biologic product (but not for a merely “biosimilar” biologic product) without the intervention of the prescribing physician. In addition, a number of state laws address issues of notification and substitution, either generally in the context of prescribed medicines or, as a growing trend in recent years, in a manner specific to biosimilars. (See “State Legislation” below.)
- **Exclusivity.** The federal legislation that authorized the approval pathway for biosimilar biological products prohibits the approval of an application for a product as either “biosimilar” or “interchangeable” until 12 years from the date on which the predecessor product (known as the “reference product”) is first approved. Some stakeholders and policymakers have advocated for a shorter exclusivity period, while others believe that the 12-year period is important as a way to protect and encourage incentives to research and develop innovative treatments.
- **Access.** With the approval of any new medicine comes the closely related policy question of whether and how the medicine will be covered by patients’ health insurance plans. Biologic medicines often are placed on plans’ “specialty” tiers, where high cost-sharing responsibilities and potential utilization management requirements (such as prior authorization) may apply. The coverage and cost-sharing policies that plans implement for biosimilar biologic medicines will have significant implications for patients’ ability to access and afford these therapies.

- **State Legislation.** In addition to activity at the federal level, a number of states have begun to implement or explore policies specific to biosimilars. These state laws may affect, for example, the manner in which health plans cover or pay for biosimilar biological products. Some state laws also address the conditions under which a pharmacist may, or may not, substitute an FDA approved “interchangeable” biological product—for a prescribed brand-name biological product.

As one example, Indiana enacted legislation in 2014 that does not allow for substitution unless all of the following criteria are met: (1) the FDA must determine that the biosimilar biological product is “interchangeable” with the prescribed product; (2) the prescriber must allow for substitution by including “may substitute” on the prescription; (3) the pharmacist must notify the patient of the substitution; (4) the pharmacist must notify the prescribing doctor of the substitution; and (5) both the pharmacy and the prescribing doctor must keep a record of the substitution for at least five years.

Glossary:

Adverse event: an undesirable, unpleasant, or life threatening reaction to a medicinal product.

Antibody (pl: antibodies): Antibodies (also known as immunoglobulins, abbreviated to Ig) are proteins that are found in blood or other bodily fluids. Antibodies are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses.

Automatic substitution and substitution: The practice by which a product other than the one specified on the prescription is dispensed to the patient, without the prior informed consent of the treating physician. A variation of substitution is practiced in some countries where, if the physician prescribes by international non-proprietary name (INN), the pharmacist may dispense any product with the same active ingredient.

Autoimmune: an immune system response that targets one’s own cell, tissue and organ. A certain level of autoimmune response is normal.

Autoimmune disease: a disease or syndrome that occurs when an autoimmune response turns pathological and causing inflammation and damage to cells, tissue and organs.

Biologic: A product derived from a living organism (from plants, animal, humans or other biological sources) that is used in the diagnosis, prevention or treatment of disease.

Biosimilar: A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.

Biotechnology: Technology based on biology, especially when used in agriculture, food science and medicine. The United Nations Convention on Biological Diversity defines biotechnology as “any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.”

Chemical drug or chemical medicine: Refers to medicines that are manufactured without the involvement of living organisms and are referred to as small molecule drugs.

Clinical trial: A study in which a drug or biologic is given to humans to establish how it works in the body and measure the nature and extent of any intended or unintended consequences as well as to determine efficacy.

Comparability exercise: The head-to-head comparison of a biotherapeutic product with a licensed originator product, with the goal of establishing similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures.

DNA (Deoxyribonucleic Acid): DNA is a nucleic acid that contains the genetic information used in the development and functioning of all cellular organisms. Molecular systems interpret the sequence of these nucleic acids to produce proteins.

Efficacy: The desired results that a medicine or treatment has when administered to a human.

U.S. Food and Drug Administration (FDA): The federal agency responsible for evaluating marketing applications and/or otherwise regulating the U.S. marketing of medicinal products, medical devices, food and cosmetics to be approved in the United States.

Gene splicing: technique for inserting material from two or more genes into another gene to produce a unique protein.

Generic medicine: A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. A generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as “therapeutically equivalent” can be expected to have equal effect and no difference when substituted for the brand name product.

Immune system: The collection of collaborating mechanisms within the body that protect against disease by identifying and attacking foreign substances in the body.

Immunogenicity: The ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T-cell response, allergic or anaphylactic reaction).

INN (International non-proprietary name): Allocated by the World Health Organization, an INN identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name.

Innovator: Describes a company that invested considerably in research and development to develop a new medicine through innovative technologies, such as biotechnology.

Innovator product: Original approved biologic medicine.

Interchangeability: Where two products, that are judged to be similar, can be exchanged one with another without a significant risk of an adverse health outcome.

Large molecule drugs: Are therapeutic proteins – also known as biologic medicines. Essentially, these are copies or optimized versions of endogenous human proteins.

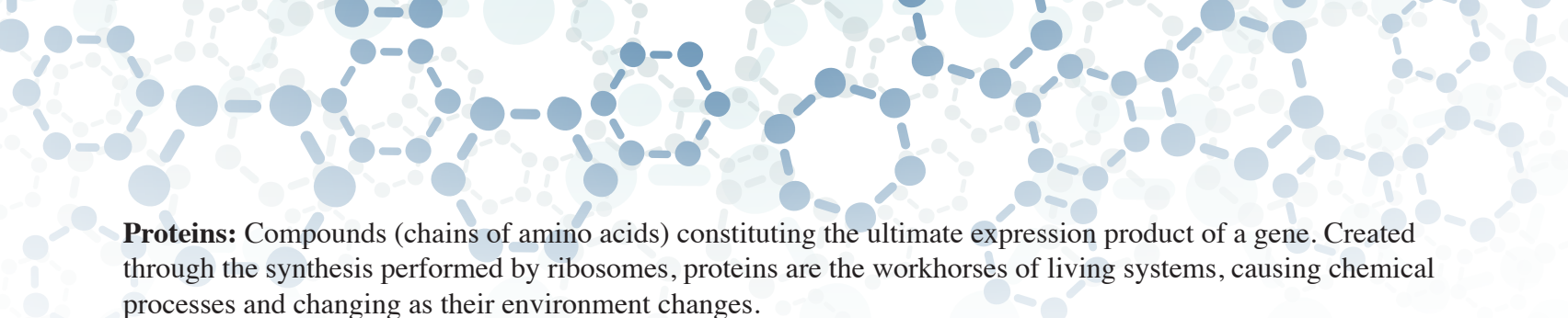
Monoclonal antibody: An antibody produced in the laboratory by a single clone of cells or a cell line and consisting of identical antibody molecules.

Pharmaceutical medicine: Also referred to as medicine or medication – any chemical substance intended for use in the medical diagnosis, cure, treatment, or prevention of disease.

Pharmacodynamics: Studies performed to determine what a drug does to the body.

Pharmacokinetics: Studies performed to determine what the body does to a drug.

Pharmacovigilance: Procedures that monitor the safety of medicines to detect, assess, understand, and prevent adverse effects or any other safety-related issue.



Proteins: Compounds (chains of amino acids) constituting the ultimate expression product of a gene. Created through the synthesis performed by ribosomes, proteins are the workhorses of living systems, causing chemical processes and changing as their environment changes.

Recombinant: In genetics, recombinant means DNA, proteins, cells, or organisms that are made by combining genetic material from two different sources. Recombinant substances are made in living cells and are being studied in the treatment of cancer and for many other uses.

Reference product: The innovator/originator product that the biosimilar product is intended to copy.

Similar biotherapeutic product (SBP): A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already-licensed, reference biotherapeutic product.

Small molecule drugs: Chemical compounds that have a defined structure and characteristics.

Switching: The decision of a physician to change a patient from one drug to another drug with the same therapeutic intent, in order to optimize therapy and reduce adverse effects.

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For more information or to order copies of this report contact the American Autoimmune Related Diseases Association (AARDA) at 22100 Gratiot Avenue, Eastpointe, MI 48021 or call 586-776-3900. www.aarda.org.



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