



A PATIENT'S GUIDE TO

Biosimilars

SECOND EDITION, 2021



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PART I Introduction

The science and policy around **biosimilars** have continued to evolve, shaping what looks to be an optimistic future for the millions of patients who would benefit from biosimilar treatments, both clinically and financially. Name brand **biologics** like Remicade and Humira are still extremely popular for treating a number of conditions including, rheumatoid arthritis, psoriasis, and inflammatory bowel disease. However, comparable biosimilars are proving to be just as effective at a cheaper cost. With all that has changed in the biosimilar landscape the past few years, we at the Global Healthy Living Foundation (GHLF) want to present our patient community with the most up-to-date developments to ensure you stay informed and ready to make the best decisions along with your healthcare **provider** regarding treatment options.

We'll still cover the basics for those who may be unfamiliar with biosimilars answering questions like, "What are biosimilars?", "Are they safe?" "How much will they cost me?" and "What's the difference between them and biologics?" along with some common terminology. From there, we'll take a dive into what the biosimilars market looks like in 2021 in the United States and abroad and what that means for you as a patient. We'll also cover important biosimilars that are already on the market or will be coming soon so that you are aware of what options are available. Furthermore, we'll detail important scientific, medical, and policy-related information to give you a breadth of understanding and hopefully increase your comfort level with the topic of biosimilars.

Every person's health, concerns, and insurance coverage are unique. While this guide will give you a general overview of biosimilars, talk with your health care professionals including your nurses, physician assistants, doctors, health insurance company, medical benefits person at your work, and pharmacists to get all your questions answered. Before you do reach out, take a look over our comprehensive list of questions (pg 15) that can be used to guide your conversations with providers. In addition to reading this patient guide, please visit creakyjoints.org for additional information on biosimilars.

PART II Patient Charter

The Global Healthy Living Foundation is a 501(c)(3) non-profit organization whose mission is to improve the quality of life for people living with chronic illnesses. Our patient charter, below, reflects our guiding principles — the deeply held beliefs that drive our community's many efforts in education, support, advocacy, and research.

WE BELIEVE:

1. The patient experience is at the heart of medicine; thus the patient must be at the center of all medical decision-making.
2. The medical process should stay between the patient and their care provider.
3. The patient should have access to all treatments deemed appropriate by their care provider.
4. Access to care should not be limited by external forces, affordability, or other factors.
5. Patients should be empowered and educated with the tools needed to make their voices heard.
6. Elected officials, insurance providers, drug manufacturers, health care professionals, and all others associated with the health care system should make it their goal to ensure the patient is the focus of all decisions.
7. The medical team should strive not only to do no physical harm to the patient, but also to do no emotional, mental, or financial harm.
8. Patients should be treated with dignity, transparency, and respect by everyone involved in the health care process.

The information in these guidelines should never replace the information and advice from your treating physician. They are meant to inform the discussion that you have with health care professionals, as well as others who play a role in your care and well-being.



This Biosimilar Guide was made possible through the support of Amgen.

PART III Understanding Biosimilars

✦ What's a Biosimilar?

To understand biosimilars, we first need to understand biologic drugs. When we think of drugs, we often think of chemical compounds like aspirin and other pills we can pick up from our local pharmacy or supermarket. Biologic drugs are a bit different. They are proteins made by living organisms, whereas traditional drugs are chemicals, referred to as **small molecules**. Biologic drugs are much larger than small-molecule drugs like aspirin.

Biosimilars are not new drugs, but rather they are copies of biologic drugs that have been used to treat many diseases and conditions, such as rheumatoid arthritis, psoriatic arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, ulcerative colitis, diabetes, multiple sclerosis, and some types of cancer. This guide will focus on biosimilars used to treat autoimmune conditions.

A biosimilar is a drug that is approved because it is highly similar in quality, safety, and efficacy to a biologic product that has already been approved by the **U.S. Food and Drug Administration (FDA)**. All biosimilars are prescription drugs, meaning you cannot get them without your health care professional's prescription.

✦ The Difference Between a Biologic and a Biosimilar

A biologic is the **reference** drug or product, and a biosimilar is the copy. Hundreds of millions of people worldwide rely on biologics to manage debilitating conditions and treat serious illnesses and having biosimilars available expands these treatment options.

Each biosimilar is made using the same amino acid starting materials and the same precise, step-by-step processes as its reference drug — the well-tested, widely used biologic that has already been on the market for years.

A biosimilar is compared with its already approved reference product through an extensive array of analytical tests and clinical studies. Once it has been shown to be highly similar to the reference product, it is carefully reviewed and approved by the FDA before being released for use by patients. Biosimilars are given to patients at the same strength and dosage as the reference biologic.

✦ Why Biologics Can't Be Copied Exactly

Because of how they are developed, biosimilars are not identical copies of their reference drugs, but they're made using the exact same starting materials and similar manufacturing processes. They are designed and developed to be highly similar to the original drug, and they would not have been approved as biosimilars if they were not.

That's why they're called biosimilars: They're made of biologic materials (bio-) and are highly similar to an approved, widely tested, and prescribed biologic.

◆ Biosimilars vs. Generic Drugs

When we talk about biosimilars, it is also important to talk about and distinguish them from **generics**. For many years, generic medicines have been available as less expensive alternatives of pills — small-molecule brand-name drugs. If it helps, think of biosimilars as generic biologics — large-molecule drugs that are injected or infused. Calling a biosimilar a generic biologic is not scientifically accurate, since a generic small-molecule drug has the same chemical structure as the original drug and a biosimilar may not. A pill containing a generic version of its active ingredient may have different inactive ingredients than the branded small-molecule drug, but the active ingredient is identical to that of the branded small-molecule drug.

Small-molecule drugs are smaller and less complex chemicals than biologics, which means that the chemical synthesis process used to create generic medications cannot be applied to the development of biosimilar medicines. Small-molecule generic drugs are created by mixing chemicals, whereas biosimilars, like biologics, are produced by living cells.

Biosimilars have slight structural differences from their **originator** biologic. A generic of a synthetic, small-molecule drug, on the other hand, has the same active ingredient as the brand-name drug and is considered bioequivalent. It is nearly impossible to replicate a biologic to produce a generic form because biologics are complex large-molecule drugs.

Some people think the difference between generics and biosimilars is that generics are exact copies of their small-molecule drugs while biosimilars are only similar. This is not true. Generic drugs have leeway in matching their branded counterparts, just as biosimilars do. The term generic biologics is becoming more popular among patients, and it may be easier for you to understand biosimilars by calling them generic biologics. However, biosimilars are different from generics because of the size and complexity of the proteins involved, as well as their manufacturing and FDA approval processes. You can read more about the FDA approval process on page [10](#).



While generics are close copies of brand-name drugs, biosimilars may differ slightly more from the reference products because of their complex proteins. A biosimilar and a generic are alike in four main ways:

1. They are both versions of a brand-name drug.
2. They become available after the original drug loses its exclusive patent.
3. They may cost less.
4. They are both approved through shorter pathways that avoid duplicating costly clinical trials.



✦ Immunogenicity

Immunogenicity refers to the potential for the body to have an immune reaction in response to a biological product, which may result in decreased **efficacy** of the product. Most biopharmaceuticals elicit an immune response. However, the resulting antidrug antibodies do not usually result in loss of efficacy. Biological products, including both reference biologic products and biosimilar products, may be immunogenic. It is important to note that biosimilars are expected to have similar or lower immunogenicity than their reference products.

Biosimilars try to match their reference products but identical copying is not usually possible, in part, because the original biologic itself may vary over time. Slight differences in a reference product are expected to occur over time and these differences are acceptable as long as they fall within predetermined ranges. The FDA carefully evaluates any differences between a proposed biosimilar product and its reference product to ensure that the biosimilar meets its high standards for approval.

PART IV Biosimilar Medication Overview

◆ Biosimilars Currently Available on the U.S. Market

The first biosimilar was launched in the U.S. in 2015. To date, the FDA has approved 30 biosimilars, the majority of which are indicated for cancer. As of now, there are 15 biosimilars approved for use in the U.S. for patients with inflammatory diseases, but only six are available, in part because of court disputes among manufacturers. As the disputes are settled, more biosimilars will be introduced in the U.S. market in the next few years.

Regardless of whether you choose to take a biosimilar or a reference product (biologic), or whether your insurance company chooses for you, it is important to know the name of the medication you take. Biosimilars are typically referred to by two different names: the brand name and the core scientific name for the reference product, followed by a four-letter suffix. There may be multiple biosimilars for one reference biologic, so by knowing the exact name of your medication, you can be clear when discussing your treatment plan with your provider, caregiver, and pharmacist.

Here are the FDA-approved biosimilars that are available for autoimmune diseases like arthritis, psoriasis, inflammatory bowel disease, and vasculitis.

Biosimilar Product	Reference Product	Approved to Treat These Conditions
Infliximab-dyyb (Inflectra) Manufacturer: Celltrion/ Pfizer	Infliximab (Remicade) Manufacturer: Janssen	<ul style="list-style-type: none">Moderately to severely active Crohn's diseaseModerately to severely active pediatric Crohn's diseaseModerately to severely active ulcerative colitisModerately to severely active pediatric ulcerative colitisModerately to severely active rheumatoid arthritisActive psoriatic arthritisActive ankylosing spondylitisChronic severe plaque psoriasis
Infliximab-abda (Renflexis) Manufacturer: Samsung Bioepis/Merck	Infliximab (Remicade) Manufacturer: Janssen	
Infliximab-axxq (Avsola) Manufacturer: Amgen	Infliximab (Remicade) Manufacturer: Janssen	
Rituximab-abbs (Truxima) Manufacturer: Teva/ Celltrion	Rituximab (Rituxan) Manufacturer: Genentech	<ul style="list-style-type: none">Moderately to severely active rheumatoid arthritisNon-Hodgkin's lymphomaChronic lymphocytic leukemiaGranulomatosis with polyangiitis and microscopic polyangiitis
Rituximab-pvvr (Ruxience) Manufacturer: Pfizer	Rituximab (Rituxan) Manufacturer: Genentech	
Rituximab-arxx (Riabni) Manufacturer: Amgen	Rituximab (Rituxan) Manufacturer: Genentech	

✦ Biosimilars Coming Soon

Here are the biosimilars for inflammatory conditions that are approved but not yet on the market or available to patients:

Biosimilar Product	Reference Product	Availability	Approved to Treat These Conditions
Infliximab-qbtx (Ixifi) Manufacturer: Pfizer	Infliximab (Remicade) Manufacturer: Janssen	No plans to launch in the U.S.	<ul style="list-style-type: none"> Moderately to severely active Crohn's disease Moderately to severely active pediatric Crohn's disease Moderately to severely active ulcerative colitis Moderately to severely active pediatric ulcerative colitis Moderately to severely active rheumatoid arthritis Active psoriatic arthritis Active ankylosing spondylitis Chronic severe plaque psoriasis
Etanercept-szsz (Erelzi) Manufacturer: Sandoz	Etanercept (Enbrel) Manufacturer: Amgen	Expected 2029	<ul style="list-style-type: none"> Moderate to severe rheumatoid arthritis Moderate to severe plaque psoriasis Psoriatic arthritis Ankylosing spondylitis
Etanercept-ykro (Eticovo) Manufacturer: Samsung Bioepis	Etanercept (Enbrel) Manufacturer: Amgen	Unknown	<ul style="list-style-type: none"> Moderate to severe polyarticular juvenile idiopathic arthritis
Adalimumab-fkjp (Hulio) Manufacturer: Mylan/Fujifilm Kyowa Kirin Biologics	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	<ul style="list-style-type: none"> Moderate to severe rheumatoid arthritis Moderate to severe chronic plaque psoriasis Psoriatic arthritis Ankylosing spondylitis Moderately to severely active Crohn's disease
Adalimumab-afzb (Abrilada) Manufacturer: Pfizer	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	<ul style="list-style-type: none"> Moderately to severely active pediatric Crohn's disease Moderately to severely active ulcerative colitis Moderately to severely active pediatric ulcerative colitis
Adalimumab-bwwd (Hadlima) Manufacturer: Samsung Bioepis	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	<ul style="list-style-type: none"> Moderate to severe polyarticular juvenile idiopathic arthritis Intermediate, posterior, and panuveitis
Adalimumab-adaz (Hyrimoz) Manufacturer: Sandoz	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	<ul style="list-style-type: none"> Moderate to severe hidradenitis suppurativa

Biosimilar Product	Reference Product	Availability	Approved to Treat These Conditions
Adalimumab-adbm (Cyltezo) Manufacturer: Boehringer Ingelheim	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	<ul style="list-style-type: none"> Moderate to severe rheumatoid arthritis Moderate to severe chronic plaque psoriasis Psoriatic arthritis Ankylosing spondylitis Moderately to severely active Crohn's disease Moderately to severely active pediatric Crohn's disease Moderately to severely active ulcerative colitis Moderately to severely active pediatric ulcerative colitis Moderate to severe polyarticular juvenile idiopathic arthritis Intermediate, posterior, and panuveitis noninfectious uveitis Moderate to severe hidradenitis suppurativa
Adalimumab-atto (Amjevita) Manufacturer: Amgen	Adalimumab (Humira) Manufacturer: AbbVie	Available 2023	

PART V Approval Process and Standards for Biosimilars

✦ How Biosimilars Get Approved

The development and production of biosimilars must follow the strict regulations of the Biologics Price Competition and Innovation Act (**BPCIA**), a part of the Affordable Care Act, or Obamacare. The BPCIA set up the system for developing and approving new biosimilars. Biosimilars are manufactured using a process similar to that used to produce the biologic drugs upon which they are based. They are highly similar to their reference drugs, so they have the same effect on you: They treat your disease safely and effectively.

When a manufacturer creates a biosimilar, it must do tests to show that the biosimilar has the same exact protein structure and works the same way as its reference drug does. Biosimilar manufacturers perform these tests to prove that the new product has the same sequence of amino acid building blocks as the original drug, and that its active ingredients work the same way. If there are any differences between the two drugs' inactive ingredients, the biosimilar's manufacturer has to prove that these very slight differences don't affect how safe or effective it is.

The goal is to establish biosimilarity between a proposed product and a reference product, not to re-establish safety and efficacy. Approval of a biosimilar product is based on review of all of the evidence submitted by the applicant, integrating various types of information to provide an overall assessment that the proposed product is similar to the reference product.

This shortened approval pathway for biosimilars does not mean a lower approval standard. The data required for an approval is extensive and, if the manufacturer can prove similarity, we can rely on the existing knowledge and experience about the safety and effectiveness of the reference biologic to support use of the biosimilar. With both generic and biosimilar drugs, scientists already know the properties of the branded, or reference drug, so it's not necessary to start over with traditional clinical trials to assess efficacy in each indication in which the reference drug is used. There are additional requirements, however, for biosimilar approval.

✦ FDA Requirements for Biosimilars

To be approved by the FDA, a biosimilar application needs to include certain types of information about the biosimilar product. The manufacturer must submit data comparing the biosimilar to its reference product. This usually includes data from:

- ▶ Analytical studies demonstrating that the biological product is highly similar to its reference product, notwithstanding minor differences in clinically inactive components
- ▶ Animal studies, including an assessment of toxicity
- ▶ A clinical study or studies that demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed

The FDA evaluates each biosimilar on a case-specific basis to determine what data are needed to demonstrate biosimilarity and which data elements can be waived, if deemed scientifically appropriate.



This guide focuses on biosimilars in the U.S., which are approved by the FDA, but it is also helpful for context to take a look at approval bodies in other countries. The key principles used to evaluate biosimilars are shared among regulators across the globe.

European Union: The European Medicines Agency (EMA) is responsible for evaluating biosimilars in EU countries. The EMA evaluates biosimilars according to the same standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines approved in the European Union. The EMA requires manufacturers of biosimilars to use comprehensive comparability studies to demonstrate the similarity between the biosimilar and the reference product.

Requirements for the biosimilar:

- It must be highly similar to the reference medicine, notwithstanding natural variability inherent to all biological medicines.
- There are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality, and efficacy.

Once the biosimilar is on the market, its safety is monitored in the same way other medicines are.

United Kingdom: Following the United Kingdom's departure from the EU, new guidance has been drafted for the approval of biosimilars. The U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) began regulating biosimilars in January 2021, according to the same principles that were previously used. Ireland has an extra layer of regulatory complexity as EU pharmaceutical law will continue to apply there.

The MHRA has proposed some changes to the EMA's approach in the draft guidance. The MHRA proposes that in most cases, a comparative efficacy trial is not necessary when there is a well-argued justification; the draft guidance states that in vivo studies (studies performed in living organisms) in animals are not relevant for showing comparability between the biosimilar and the reference products; and the MHRA indicated it may be willing to accept real-world evidence to support regulatory submissions.

Canada: In Canada, biosimilars are evaluated and authorized by Health Canada. Manufacturers must provide information to Health Canada that demonstrates the similarity between the biosimilar and its reference biologic. Manufacturers must demonstrate similarity through comparative studies, which is done using a stepwise approach. The manufacturer begins with structural and functional studies, then continues with clinical studies in humans.

Requirements for the biosimilar:

- The biosimilar and the reference biologic drug must be highly similar.
- There are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug.

Once the biosimilar is approved, it is continually monitored for safety in real-world settings. Health Canada requests that manufacturers submit a Risk Management Plan (RMP), which sets a process for monitoring the

biosimilar's safety. The RMP will generally include monitoring and risk-minimization activities that are like those in place for the reference biologic.

Australia: As with all medicines in Australia, biosimilars are evaluated by the Therapeutic Goods Administration (TGA). The TGA has largely adopted international guidelines from the EMA, which outline the quality, nonclinical, and clinical requirements for biosimilars. To gain TGA approval, a biosimilar must be evaluated using clinical, and laboratory-based comparability studies to demonstrate similarity in quality, safety, and efficacy to the reference biologic.

Requirements for the reference product:

- The reference biological medicine must be a biological medicine that has been registered in Australia (or a similarly regulated country) based on full safety, effectiveness, and quality data.
- The reference biological medicine must have been marketed in Australia long enough for there to be a substantial body of acceptable data regarding its safety and effectiveness.

Requirements for the biosimilar:

- The similarity of the biosimilar medicine to the reference biological medicine needs to be demonstrated through analytical, laboratory, and clinical studies.
- The information from these studies is sent to the TGA for review to ensure that the biosimilar is highly similar to the reference product, and that similar outcomes for benefits and risks are expected. Once the biosimilar is approved, it is continually monitored for safety in real-world settings. The manufacturer must submit regular reports known as Periodic Safety Update Reports to the TGA with detailed information and safety data.

◆ Extrapolation of Indications

For a biosimilar, equivalent effectiveness and comparable safety need to be demonstrated in a clinical trial in only one disease, rather than in each disease for which approval is sought, since the effectiveness of the reference product has already been proved in each of these indications. That means if the original branded biologic is approved for more than one disease — such as rheumatoid arthritis and ankylosing spondylitis — the biosimilar may be approved for those indications too. That's because the reference drug has already been tested and approved for treatment of those diseases. This is known as **extrapolation** of indications — when a biosimilar is approved for an indication that is approved for the reference product even if the biosimilar has not been studied in that indication. The idea is that there is no need for a biosimilar to duplicate clinical trials in patients with every disease, which saves time and money.

◆ Interchangeability

You may be wondering, “Will my pharmacist substitute the less expensive biosimilar for a biologic in the same way that they could with a generic?” The answer is only if they have been approved as being **“interchangeable.”** Only one biosimilar insulin glargine (a biosimilar of the reference product Lantus) has been approved as being interchangeable. Otherwise, you must have a prescription specifically written by your provider for a biosimilar in order to receive it. However, your insurance company may require that you be switched to a biosimilar. This is starting to happen.

You still have the option to stay on the reference biologic, if you can pay the increased cost set by the insurer for the reference product. However, most people cannot.

In the future, pharmacists may be able to substitute other biosimilars for their reference products without provider approval, similar to how they can substitute generics for small-molecule brand-name drugs. This is known as interchangeability. An interchangeable biosimilar is one that, according to the strict rules and definitions of the BPCIA, must have undergone additional testing — beyond that required to demonstrate biosimilarity — to show that it can be substituted for the reference product by your pharmacist without having to involve the health care professional who prescribed it.

According to BPCIA laws, any drugmaker that develops a biosimilar and wants to apply for it to be labeled as being interchangeable must provide additional data to show that, if a patient is switched back and forth at least three times between the biosimilar and its reference drug, there will be no differences — no risk of any changes — in safety and effectiveness. Only one biosimilar, insulin glargine, has been designated as interchangeable.

Without this interchangeability designation, the pharmacist must call in advance and get permission from your provider to dispense a biosimilar in place of an originator. With an interchangeability designation, the pharmacist does not need to obtain permission in advance.

One possible concern about interchangeable biosimilars is that your doctor or other prescribers might not be told if your pharmacist fills your prescription with the interchangeable biosimilar instead of the reference biologic. However, state laws about interchangeability specify that such notification must occur within a short time after the substitution has been made. Although the FDA is responsible for designating interchangeability, it is regulated through individual U.S. state laws, similar to those that regulate interchange between brand-name and generic prescription drugs. A majority of the states have revised their laws regulating generics to address biosimilars. Currently, 45 states and Puerto Rico have laws that address biologics and biosimilar substitution.

✦ **Biosimilar Safety**

Biosimilars are absolutely safe to use. Every drug that has been approved for your use by the FDA must meet very high standards of safety. This includes all biosimilars and biologics. They are prescription drugs so, in the U.S., the FDA regulates how they are manufactured and delivered to you.

While biosimilars follow a shorter track to FDA approval, their makers still must test them thoroughly to show that they're highly similar in structure and function to their reference products, that they're safe, and that they work to treat diseases as they should.

PART VI Starting on a Biosimilar — What Do Patients Need to Know?

✦ Who Should Take a Biosimilar?

It is normal to have concerns about receiving or switching to a new medication, including a biosimilar. You may have questions about its safety, whether it will be as effective as the originator biologic, or if it will be administered differently. Below, we offer questions you can ask your provider to ensure that you have all the answers as you work to decide together if a biosimilar is right for you.

The short answer to “Who should take a biosimilar?” is anyone for whom the biosimilar is indicated and who has not previously failed its reference product. Since biosimilars must demonstrate that they are safe and effective in order to be approved, patients can expect to experience the same effects with a biosimilar as they would with a reference product.

Biosimilars can increase access to treatment for many patients by providing more options, potentially at a lower cost. Having treatment options is very important for people with serious health conditions like psoriasis, inflammatory bowel disease, inflammatory arthritis, or vasculitis. If you are struggling with the cost of your treatments, depending on your insurance, biosimilars may be a good option for you to consider. Talk to your provider and pharmacist about what you can expect the cost to be.

✦ Is It Safe to Take a Biosimilar If I Started Treatment on the Reference Product First?

Generally, biosimilar medications can be used if you have been treated first with the reference product. Research shows that you should be able to switch from the original biologic to a biosimilar without problems. Your disease signs and symptoms should be controlled in the same way, and you should not experience new side effects from the biosimilar. Always talk to your health care provider about available treatment options and their potential risks and benefits.

✦ Choosing a Biosimilar: Injection vs. Infusion

Each biosimilar is administered in the same way as its reference product, with the same dose and frequency. Currently, no injectable biosimilars for inflammatory diseases are available in



Something to Consider: The Nocebo Effect

When patients anticipate a negative response from a change in medication, they may experience an increase in symptoms. This is known as the **nocebo effect**. It's the opposite of the placebo effect — where you think the medication will work and it does, even if it's a sugar pill. That's why educational materials like this guide are so important. The best way to combat the nocebo effect is to learn about drugs and other treatments, including information about their safety and efficacy. Another important step to avoid the nocebo effect is to have open conversations with your provider about your concerns and desires for your treatment. This way you can work together to ensure that you continue to feel good.

the U.S., so if you are considering taking a biosimilar, it will be an infusion. An infused drug is one that is given through an intravenous (IV) drip, typically in a hospital, at your provider's office, or at an infusion center.

If you use an infused drug like Remicade or its biosimilars, you go either to a hospital or to your provider's infusion clinic. The provider or hospital buys the drug and submits a bill to the health-benefits department of your health insurance company. It is expensive to keep a stock of these drugs, so many small infusion centers offer only one brand. If your insurance company covers a different brand, you might have to go to another infusion center or hospital to get the drug that's covered. If you are receiving Remicade, you may not be able to switch to a biosimilar because your infusion center may not stock it. Whether you and your provider decide to switch to a biosimilar or start on one as your first biologic treatment, you may have to travel to have it infused.



Questions to ask your provider about starting on an infusion biosimilar:

- Which infusion medication will I get?
- How long does an infusion take?
- How does getting the infusion work exactly?
- Where can I get the infusion?



✦ How to Talk to Your Provider

Enhanced communication between you and your provider can help you successfully switch to a biosimilar. **Shared decision-making** is when your provider describes known benefits and risks of the options, you express your preferences, and together you decide on a path forward. Shared decision-making can improve the satisfaction you feel as a patient because you are an active participant in your care. It can also strengthen the trust between you and your provider and, in turn, improve health outcomes, since you feel confident in the decisions being made about your care. Open discussion is encouraged when you are deciding whether to start a biosimilar. You can use the glossary at the end of this guide to help you communicate and handle the technical language.

Here are questions to ask your provider if you are considering trying a biosimilar:

BENEFITS:

- ▶ What benefits can I expect from a biosimilar?
- ▶ Were clinical trials conducted in patients like me comparing the biosimilar to its reference biologic?
- ▶ If clinical trials were not conducted in patients like me, what is the evidence that the biosimilar would work the same as the original biologic for patients like me?

SIDE EFFECTS:

- ▶ What side effects can I expect, and how difficult or serious might these be?
- ▶ How likely is it that I will have the same and not worse side effects with the biosimilar as with the original biologic?

SUPPORT:

- ▶ Is there a support website, phone line, or email address for the biosimilar manufacturer if I have questions or concerns?
- ▶ How will I take the biosimilar? The same way I take the original biologic now?
- ▶ Is support available to help me find an infusion center if I'm not currently being infused?
- ▶ When injectable biosimilars are available, will ordering and receiving them at home be the same? Will monitoring be the same?
- ▶ What is the dosing schedule?
- ▶ Will I be able to get the biosimilar at the same pharmacy?
- ▶ How often do I need to have blood work done?

PLANNING:

- ▶ How will I know if the biosimilar is working for me? What additional monitoring, if any, is provided?
- ▶ If I feel the biosimilar is not working as well as the original biologic, can I go back on the original biologic?

Here are questions to ask your insurance provider if you are considering trying a biosimilar:

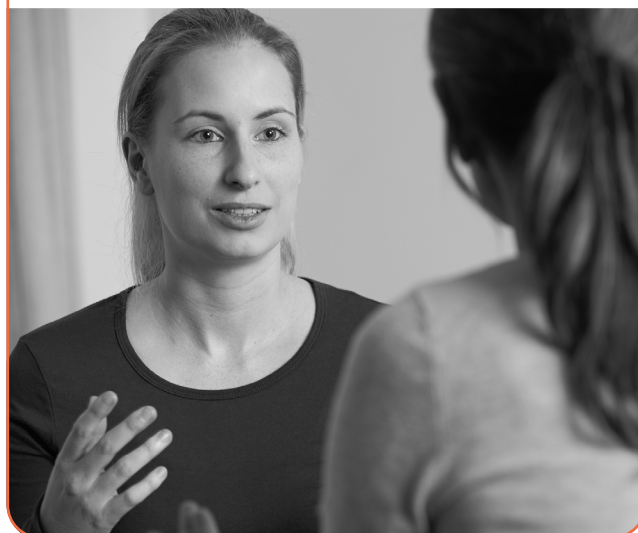
COST:

- ▶ What is the cost difference between the biosimilar and the original biologic?
- ▶ What are the cost savings to me?



If you are considering starting a biosimilar:

- **Talk to your provider.** Find out if there is a biosimilar available, and if your provider thinks it may be right for you.
- **Find out if your insurance plan covers the biosimilar.** If it doesn't, ask to be notified when coverage for a biosimilar becomes available.
- **Get specifics from your provider and pharmacist.** Ask them to explain how the biosimilar will work as part of your treatment plan. Ask any questions that you have about its safety, effectiveness, and cost.



✦ Treatment Plan

Deciding on a treatment plan for your disease is complex. Having access to reliable information helps you make a treatment plan.

Ultimately, you and your provider will work together to determine your treatment plan. Your provider will explain the medications available to you, the evidence for their use, and their risks and benefits. You'll be asked about your preferences, treatment goals, and life circumstances. Issues you might raise in this discussion could be about the cost of a particular treatment, how a medication is delivered (injection vs. infusion), and medication side effects. Together, you and your provider will come up with a plan that takes your needs and preferences into account.

✦ What Happens If a Biosimilar Isn't Working?

If you think you are not responding to the biosimilar, talk to your provider about your concerns. Together, you can determine if you should wait longer to see results or if this treatment plan is not right for you.

Here are a few questions you can think about and bring up with your provider:

Benefits: What have been the benefits of the biosimilar?

Adverse effects: What side effects have I experienced, and how serious or difficult have these been to tolerate?

Effectiveness: How do I know if the drug is working? How have we monitored the effectiveness of the drug and its side effects?

PART VII Biosimilar Uptake

✦ Environment in the U.S.

The U.S. government has been eager for biosimilars to function as lower-priced versions of costly brand-name biologics to treat debilitating and life-threatening diseases. Biosimilars are projected to save the health care system as much as \$54 billion over the next 10 years. Most of these savings are projected to go to Medicare, Medicaid (perhaps reducing taxes), and employers (perhaps reducing employee insurance premiums), but not directly to patients.

For patients with inflammatory diseases, significant barriers have stood in the way of biosimilar success in the U.S. In the immunology market, biosimilars make up less than 15 percent. What's hopeful is that we've seen oncology biosimilars claim a significant share of their market, giving confidence to biosimilars. Recently launched biosimilars to treat patients with inflammatory diseases are being introduced at more competitive prices and have been gaining market share. In the next few years, as more biosimilars become available, there will be more competition, which should bring down prices of some of the best-selling medicines.

Some of the barriers that have stood in the way of the success of biosimilars in the U.S. are outlined below.

There have been delays in the commercial availability of biosimilars, often due to patent disputes, settlements, and other legal issues. For a biosimilar to enter the market, all of the multiple patents on the reference biologic must expire. Although the biosimilar may already have been approved by the FDA, this delays market entry of the biosimilar.

Data suggest that clinicians are hesitant to prescribe biosimilars. This creates a problem because biosimilars can enter the market and lower costs only if they are being prescribed. Physicians might be hesitant because they may not understand the rigor of the biosimilar approval process, because they might consider that the economics of biosimilars are not favorable enough, or because they are used to their prescribing patterns with reference biologics and are resistant to change. Increased, in-depth education about biosimilars could help providers to become more comfortable and willing to prescribe them. The same is true for patients: biosimilars can enter the market only if patients are willing to take them. Patient education about biosimilars is important. Patients may play a large role in influencing their health care team to prescribe biosimilars. Patient demand drives many prescriptions, as evidenced by the amount of direct to consumer drug advertising.

Health plan benefit design have an impact on the biosimilar market as well since health plans decide what drugs are on their list of available drugs (a **formulary**), at what cost, and how available they are to patients. Insurance companies (often called **payers**) want to see biosimilars discounted as much as 40 to 60 percent to offset the already deep discounts and rebates they receive from manufacturers of reference biologics. Therefore, although biosimilars have been developed to be available to patients at a lower cost, payers and health plans may not offer biosimilars as a

first-line option for patients or include them on their formulary at all.

Since biosimilars have been available in the U.S. only since 2015, the time frame to evaluate their impact has been short. If their use grows over the next decade, as is predicted, this could result in substantial savings to the health care system and allow expanded access to treatments for patients. Insurers may offer price incentives to patients for using biosimilars, as they have done for using some generic drugs.

✦ **How Does the Market Relate to Me as a Patient?**

Many biosimilars are struggling to gain market share. Because of this struggle, they may not be available to you or cost less as might be expected. Biosimilars have lowered the cost of treatment by creating market competition for brand-name biologic medications. That provides patients like you with more treatment options — biologics and biosimilars — and has already lowered the cost of both. But since the approval of a biosimilar does not usually result in its immediate launch or inclusion by insurance companies on their list of preferred drugs, market competition is delayed and expected savings reduced.

Hopefully, as use and approval of biosimilars continues to grow in the U.S., the resulting savings will be shared with patients, enabling more patients to have access to these safe and effective treatments and improved health outcomes. As more biosimilars are approved and become available, market competition will increase and prices will continue to come down. The average sales price of the popular infused drug Remicade has dropped nearly 33 percent since its biosimilar counterparts became available. However, direct savings to you may not be as much as you'd like. The future of biosimilar sales depends on market dynamics, including price negotiations with payers, prescribing by providers, and acceptance of biosimilars by patients.

✦ **Environment Outside the U.S.**

The first guidelines for the review and approval of biosimilars were developed by the European Medicines Agency in 2005. The World Health Organization (WHO) first published its guidelines in 2010, followed by the U.S. FDA in 2012. Globally, other regulatory authorities have developed or are evolving approval guidelines and pathways for biosimilars.

In Europe, where biosimilars have been on the market since 2006, they typically cost 10 to 30 percent less than their reference biologics. While most European countries have health care systems that are very different from that in the U.S., it is helpful to look at their cumulative experience which provides information about safety and efficacy in real-world settings and about the potential savings from use of biosimilars. It is also important to recognize other factors that have led to the success of biosimilars in Europe. In addition to market competition, success can be attributed to educational programs about biosimilars for providers and patients, and the fact that a single purchaser — the government — often makes all health care available for free or at very little cost to the patient.

In other countries around the world, biosimilars are also steeply discounted. For example, the cost

of biosimilars in Japan is up to 67 percent lower than that of their reference products. In South Korea, reference biologics are losing market share as their biosimilars become available. Use of biosimilars is an integral component of worldwide efforts to reduce the high cost of brand-name biologics and improve patient access to effective treatments at a lower cost.

PART VIII Biosimilar Costs

✦ Are Biosimilars Less Expensive?

The concept supporting the creation of biosimilars is that, if a biologic drug that went through years of expensive development and testing works well and is safe to use, a copy using similar manufacturing processes could be developed faster and more economically because it would not have to prove again that it works in all the diseases for which its reference drug is already approved. Thus, biosimilars should cost consumers less because they cost their manufacturers less to develop and test. However, this depends upon whether your insurance company will pass on these savings to you.

Biosimilars have the potential to reduce health care costs while also increasing access for patients. The RAND Corporation estimated that biosimilars would reduce direct spending on biologic drugs by \$54 billion between 2017 and 2026. Although biosimilars have been available in the U.S. since 2015 and have yielded savings for the health care system, they have yet to achieve the savings predicted. Patients themselves have not yet realized direct savings. Health insurance companies have indicated that the lower price, while not passed on to patients, helps to keep the price of premiums low, but patient premiums, deductibles, and copays have all risen. However, it is worth noting that experts say that there hasn't been nearly enough time to analyze and determine what savings biosimilars can generate. Researchers continue to believe that biosimilars could meet the RAND Corporation's estimate.

✦ Do Biosimilars Save Money?

Biologics are among the most expensive prescription drugs in the United States, which poses many barriers to patients accessing necessary treatments. In the U.S. to date, biosimilars have generated limited savings compared with expectations. Biosimilars are not like generics when it comes to patient savings. When a pill has a generic alternative, you often can save a substantial amount of money by switching from the brand name to the generic. This has not been the case with biosimilars. Health insurance companies, so far, have not shared these savings with patients.

Manufacturers of biosimilars have priced these drugs lower than their reference products. For example, infliximab-dyyb (Inflectra) was introduced at a list price that was 15 percent lower than that of infliximab (Remicade). While this may seem encouraging, manufacturers have not been aggressive enough with their pricing of biosimilars when they enter the market. Generic drugs are typically sold at a price that is 80 percent to 85 percent lower than their brand-name medicines and, while biosimilars are more expensive and complex to produce than generics, there have been similar substantial savings in research and development costs. It appears that biosimilar manufacturers are moving in the right direction: Infliximab-axxq (Avsola) was introduced in 2020 at a list price which was 57 percent less than that of infliximab (Remicade).

However, the cost of a drug to you, the patient, is that of your deductible and copay, not the retail

price of a drug. Expensive biologic drugs and biosimilars both can easily burn through your deductible. After that, you are responsible for paying the copayment for a biosimilar as you would for a reference biologic drug.

The list price of a biosimilar is usually lower than that of a reference biologic, but the magnitude of the price reduction varies. You are not impacted directly by the list price unless you are one of the very few people without insurance coverage who must purchase drugs at their list prices.

As more biosimilars have entered the market, the prices of reference biologics have become cheaper. Theoretically, the prices of biologics and biosimilars could someday become the same and patients could choose among them without regard to cost. However, to date, our complex health care system has prevented such cost-neutral choices from being a reality.

✦ **Employers as Stakeholders**

All stakeholders have a role in providing information, and there is great potential for joint efforts, especially for employers. Employers can negotiate with insurance companies on benefit design, and since most Americans get their health insurance through their employer, this could improve access to biosimilars.

When medically appropriate, employers could promote biosimilars as a healthy alternative to expensive biologic drugs. Employers are aware of the health care costs of their organizations and can assess their amount of spending on specialty drugs or on specific conditions. This information can be used by employers to negotiate with insurers and their partner pharmacy benefit managers regarding which drugs are offered as preferred and at what cost to the patient. In this way, employers can advocate for biosimilars when negotiating health plans by urging design of the health plan to encourage biosimilar use. They can negotiate for a biosimilar to be placed in a tier with a lower copay than its reference biologic, thus contributing to direct savings for the patient and allowing greater access to biosimilars. A recent study analyzed 13 large U.S. employers and their health plan beneficiaries and found that biosimilar use provided savings. Use of biosimilar infliximab offered a 32 percent savings compared with reference infliximab (Remicade) and yielded average savings of \$1.53 million on infliximab for participating companies. For what the patient paid, the out-of-pocket costs were significantly reduced as well. Patients taking biosimilar infliximab paid, on average, 12 percent less (about \$300 per year) in out-of-pocket costs. This study demonstrates the potential savings for both employers and beneficiaries taking biosimilars. As plan sponsors, employers can use this information to ensure that their employees have access to high quality, effective medications at affordable costs.

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Ms. Netto was diagnosed with Psoriatic Arthritis in 2019 and is currently on a biosimilar treatment. She enjoys reading, finding scenic walking trails and spending time with family and friends. Her professional background is in local government Human Resources.



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Dr. Kay is a Fellow of the American College of Rheumatology and of the American College of Physicians. In 2018, he received the Distinguished Service Award from the American College of Rheumatology and he was awarded honorary membership in EULAR. He is an ad hoc reviewer for many journals and a member of the editorial board of RMD Open.

Dr. Kay's clinical interests span the spectrum of rheumatic diseases, with special interest in rheumatoid arthritis, spondyloarthropathies, and other forms of inflammatory arthritis. He was a member of the group that

developed the 2010 ACR/EULAR Diagnostic and Classification Criteria for Rheumatoid Arthritis. He chaired the Rheumatology Working Group and was a member of the Internal Medicine and Musculoskeletal Topic Advisory Groups for the World Health Organization in its Revision of the International Classification of Diseases (ICD)-11.

Over the past three decades, his clinical research has focused on nephrogenic systemic fibrosis (formerly known as nephrogenic fibrosing dermopathy), β 2-microglobulin amyloidosis, and other rheumatologic problems of patients with chronic kidney disease. He has been a principal investigator on over 60 clinical trials of novel therapies for rheumatoid arthritis, axial spondyloarthritis, gout, and osteoarthritis. Over the past decade, he has been involved in the development of biosimilars to treat rheumatic diseases. Dr. Kay lectures internationally and is the author of more than 250 publications and book chapters.

GLOSSARY

Biologic: A drug produced by living organisms or containing components of living organisms.

Biosimilar: A biologic that has been demonstrated to be highly similar to an existing biologic in terms of quality, safety, and efficacy that has been reviewed and approved by a regulatory agency according to a dedicated pathway for biosimilar approval.

BPCIA: The Biologics Price Competition and Innovation Act; provides an abbreviated pathway for biosimilars to gain FDA approval.

Clinical trial: A research study performed to evaluate a medical, surgical, or behavioral intervention in people.

Efficacy: The beneficial clinical response achieved with a drug.

Extrapolation: The approval of a biosimilar for use in an indication held by the reference product but not directly studied in a clinical trial comparing the biosimilar to its reference product.

FDA: The Food and Drug Administration; a government agency in the U.S. that regulates approval and manufacture of foods, cosmetics, drugs, and other medical products.

Formulary: A list of prescription drugs covered by a health plan.

Generic: A small molecule drug that has the same active ingredient as an existing approved brand-name drug and has been shown in a clinical trial to have identical properties to the brand-name drug.

Immunogenicity: The ability of a substance to provoke an immune response.

Infusion: Delivery of liquid medicine through a vein.

Interchangeable product: A biosimilar that meets additional requirements outlined by the BPCIA and may be substituted for the reference product by a pharmacist without the involvement of the prescriber.

Nocebo effect: Adverse effects experienced by an individual when administered an inert substance. This term has been used to refer to the decreased effectiveness or adverse symptoms experienced by a patient due to their negative expectations regarding that treatment.

Originator biologic: A novel biologic medication that has been reviewed and approved by a regulatory agency.

Out-of-pocket costs: The patient's share of health care costs.

Payer: The entity that pays for an administered medical service. An insurance company is the most common type of payer.

Pharmacy benefit manager: A business that manages prescription drug benefits on behalf of a payer.

Provider: A healthcare professional who provides medical treatment and advice based on formal training and experience.

Reference product: An approved biologic medication to which a biosimilar candidate is compared.

Shared decision-making: A process in which both the patient and the provider contribute to the medical decision-making process by discussing and deciding upon the course of diagnostic evaluation and treatment.

Side effect: A secondary, typically undesirable, effect of a drug or other medical treatment.

Small-molecule drug: A chemical compound manufactured by chemical synthesis.

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