

Biologics & Biosimilars

WHAT YOU NEED TO KNOW
ABOUT THESE COMPLICATED
MEDICATIONS



FROM THE EXPERTS AT THE ARTHRITIS FOUNDATION



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Biologics & Biosimilars: You Have Questions, We Have Answers

IF YOU TAKE BIOLOGIC DRUGS TO MANAGE YOUR ARTHRITIS, YOU WILL BE HEARING MORE ABOUT DRUGS CALLED BIOSIMILARS — AND YOU MAY BE ASKED TO SWITCH TO ONE. HERE'S WHAT THEY ARE AND WHAT YOU NEED TO KNOW ABOUT THEM.

Many more drugs called biosimilars that treat inflammatory and autoimmune arthritis will launch in the U.S., starting in 2023. Learn what they are, how safe and effective they are, and how they compare with biologic drugs you may already take.

WHAT ARE BIOLOGICS?

Biologics are a type of disease-modifying anti-inflammatory drug that slows or stops the out-of-control inflammation that damages joints and other organs in many conditions, including autoimmune arthritis. Unlike aspirin, antibiotics and other drugs made from synthetic chemicals, biologics are produced in living organisms, like plant and animal cells, using DNA technology.

In autoimmune diseases, they target specific parts of the immune system that drive inflammation.

Biologics are much larger and more complex than chemically-derived (also called small-molecule) medicines, including nonbiologic disease-modifying anti-inflammatory drugs. They are also more sensitive to light and temperature and require special handling.

WHAT ARE BIOSIMILARS?

Biosimilars are close copies of biologics that are already approved but are manufactured by different companies. The Food and Drug Administration (FDA) requires biosimilars to be as safe and effective as the original biologic, also known as the originator or reference drug. Differences between the two aren't "clinically meaningful," which means any differences do not affect the drug's effectiveness or safety. Biosimilars have the same active ingredients as their reference biologics, work in the same way, treat many of the same diseases and have similar potential side effects.

WHAT YOU NEED TO KNOW ABOUT BIOSIMILARS



ARE BIOSIMILARS GENERICS?

No. Generics are unbranded versions of small-molecule drugs made from specific chemical components. Although the FDA allows small differences between generics and brand-name medicines, such as different shapes, colors and coatings, the chemical structure is the same. Biologics are made from unique, living organisms and differ slightly from batch to batch. Small changes can occur to proteins inside the cells or during manufacturing. These variations are normal and expected but make the drugs impossible to copy exactly.

HOW ARE THEY ADMINISTERED?

Biologics and biosimilars aren't well absorbed in the body if taken orally. They must be administered directly into the bloodstream, either through a shot at home or an intravenous infusion in a doctor's office or clinic. Biosimilars to the biologic infliximab (*Remicade*) have been given as infusions since 2016. If you or someone you know gets *Remicade* infusions, they may have received one of the biosimilars without knowing it.

Injectable biosimilars come in both pre-filled syringes and autoinjector pens. Most are citrate-free, making the injections less painful.

Biosimilar Terms to Know

Reference Product

A biologic already approved by the FDA that a biosimilar is based on.

Switching

Changing from a biologic to a biosimilar or between biosimilars with no loss of effectiveness or safety.

Interchangeability

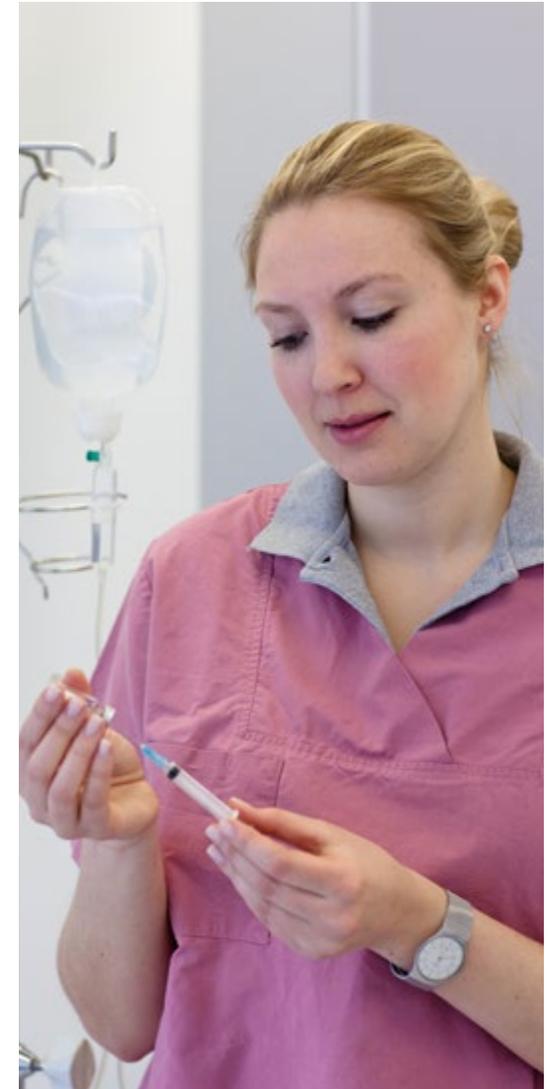
In states that allow it, a pharmacist can substitute a biosimilar for a biologic without approval from the prescriber or the patient. Interchangeable biosimilars must meet even higher standards to prove to the FDA that it is as safe and effective as its reference product. Only one arthritis biosimilar — *Cyltezo*, a biosimilar to adalimumab (*Humira*) — currently has this designation. But more are expected.

WHAT ARE THE SIDE EFFECTS?

Biologics and biosimilars have similar but not always identical side effects, and some can be quite serious. Both weaken the immune system, lowering the number of white blood cells and raising the chance of potentially life-threatening infections, especially tuberculosis and invasive fungal infections.

Other possible side effects include:

- **Sinus and upper respiratory infections.** In an older study, the biosimilar *Remsima* caused significantly more upper respiratory infections than its reference product, infliximab (*Remicade*). Other studies haven't found major differences between the two drugs.
- **Infusion or allergic reaction.** This is your immune system's response to treatment. It can happen during an infusion or a few hours or weeks later. Symptoms may include itching, rash, hives, fever or chills, nausea and headache. Trouble breathing and chest pain are less common but can be life-threatening and need immediate medical care.
- **Injection site reaction.** Swelling, redness, bruising, welts and pain can occur where a biosimilar is injected. These usually go away in a few days but may linger longer for some people. Rotating injection sites can help prevent a buildup of scar tissue, which makes shots more difficult and painful.
- **Multiple sclerosis (MS).** A 2023 Canadian study involving nearly 300,000 patients with autoimmune arthritis or inflammatory bowel disease showed a higher risk of developing MS when they were treated with biologics, especially for arthritis. The study looked only at biologics, but the findings may also apply to biosimilars. Still, the study authors say the increased risk is so small that only people who have MS or a family history of the disease should avoid these medications.



The Cancer Conundrum

Early studies found an increased risk of lymphoma and other cancers with biologics and biosimilars. Newer lymphoma research has been mixed, but many studies report a higher risk of treatable nonmelanoma skin cancer.

HOW ARE BIOSIMILARS APPROVED?

Manufacturers submit traditional chemical (small-molecule) drugs to the FDA through a new drug application (NDA) to establish that the medications are safe and effective. Generics go through an abbreviated process to show they are identical to and work just as well as brand-name versions.

The Biologics Price Competition and Innovation Act (BPCIA), part of the 2010 Affordable Care Act, established a similar abbreviated approval pathway for biosimilars, making the process easier and faster but just as rigorous. The goal is to prove similarity to the reference product in structure and function. If a biosimilar has the same protein structure and works the same way as the reference product, it should be just as safe and effective. This means biosimilars don't go through multiple rounds of pre-approval clinic trials like biologics do. If a biosimilar proves nearly identical to a drug that treats rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, for example, it only needs to show it works well for one of those conditions. It is assumed to be safe and effective for the others — a process called “extrapolation.”

WHY AREN'T MORE BIOSIMILARS AVAILABLE IN THE U.S.?

In short, because competition to existing drugs has been delayed for years through the U.S. patent system and legal obstacles. At the same time, prices on these very expensive drugs have continued rising. Once a patent on a drug expires, other companies normally would make competing medications – as happens with generics. But biologics competitors ended up in courts much longer than usual. Some of the legal disputes have finally been resolved, and in 2023, at least eight biosimilars to the world's best-selling drug, adalimumab (*Humira*), are potentially coming on the market. The first of these, *Amjevita*, became available in January 2023. Other countries, as in those in Europe, where U.S. patents don't hold sway, have had biosimilars available for years.



WILL THEY COST LESS?

Biosimilars were intended to be less expensive than the brand-name biologics, and therefore drive down costs of all biologics — which are among the most expensive drugs — making them more affordable and accessible to more patients. In the U.S., biologics drove 70% of increases in drug spending in one five-year period and account for around 40% of drug spending overall, according to a report in the *AMA Journal of Ethics*. Its lead author, Ameet Sarpatwari, JD, PhD, is principal investigator of a biosimilars market study and instructor of medicine at Harvard Medical School. The Rand Corporation in 2017 projected that biosimilars would cut these costs by about 3%, saving the health care system some \$54 billion by 2027.

Whether patients see savings depends largely on how pharmacy benefits managers (third-party companies that manage prescription drug benefits for insurance companies, large employers, Medicare and others) handle them and whether insurance companies identify them as the preferred product over the brand-name biologic in their formularies.

The hope is that as biosimilars become more accepted and competition increases, consumers and patients will see savings. But even if prices come down, they won't match the deep discounts seen with generics in the U.S. — about 85% less than the brand-name drug — or with biosimilars in countries that strictly control drug costs. In one comparative study published in *JAMA Open Network*, biosimilars with a median monthly price tag of nearly \$9,000 in the U.S. cost \$932 in Germany and \$1,351 in Switzerland.

Pricing transparency would reveal whether biosimilars will reduce costs for U.S. patients.

WHY WOULD I START OR SWITCH TO A BIOSIMILAR?

Mark Box, MD, a rheumatologist in Kansas City, Missouri, says prescribing may be driven by insurers. “Some insurance companies mandate that when we start someone on a new [biologic] we must use the biosimilar,” he explains. “Most of them are still allowing us to maintain the originator product for people who are stable on the medication. But in some cases, insurance companies are demanding that you use a biosimilar, and that’s really [about] cost.”

Historically, though, the reverse has been true — and may continue to be. One strategy drugmakers have used is to negotiate contracts ensuring that insurers lock their brand-name biologics exclusively into their formularies, or they insert clauses in contracts that a patient must “fail” a biologic before switching to a biosimilar. This might ensure supply and price stability, but it also could have the effect of quashing competition that would potentially lower prices.

The Arthritis Foundation believes the decision to switch to a biosimilar should be made by patients and their providers.



IS SWITCHING SAFE?

- In 2019, researchers published results of the first large real-world trial examining whether patients who were doing well on the originator drug *Remicade* could safely switch to its biosimilar *Remsima*. The study included 380 people with conditions *Remicade* is FDA-approved to treat, including spondyloarthritis, rheumatoid arthritis (RA) and psoriatic arthritis. The study found no difference in outcomes between *Remicade* and *Remsima* patients after a year and about the same number of side effects. A six-month extension of the trial compared people who had been on *Remsima* for a year to those who switched at the one-year mark, and also found no differences.
- Another large study compared RA patients on *Remicade* to those switching to *Remsima*. There were no differences in drug safety and effectiveness in the 54-week study or 10-month extension trial.
- A 2023 analysis of data reported by physicians and patients found that patients who didn't switch from a biologic to a biosimilar had better outcomes and were more likely to stick with treatment than those who did. However, the authors suggest that the "nocebo effect" — believing a treatment won't work — and lack of information about biosimilars may have influenced some of the poor outcomes.

The Arthritis Foundation believes biosimilars are safe and effective, as required by FDA approval standards and according to current data. We also believe health care providers have a responsibility to educate their patients about biosimilars. You can read the full Arthritis Foundation Statement on Biosimilars here: [arthritis.org/biologics](https://www.arthritis.org/biologics).

WHAT ARE INTERCHANGEABLE BIOSIMILARS?

Cyltezo, a biosimilar to adalimumab (*Humira*) launching in the U.S. in 2023, is among a handful of FDA-approved biosimilars designated as “interchangeable.” This allows pharmacists in states that permit it to substitute the biosimilar for its reference product without prior approval from the prescriber or patient, just as they often substitute generics for more-expensive brand-name drugs.

Interchangeables must meet a higher bar for FDA approval than other biosimilars do.

Drugmakers must prove that people can switch from a reference drug to its biosimilar multiple times without problems. This doesn’t mean interchangeables are better, just that they’re easier to substitute at a pharmacy. All biosimilars are approved by the FDA, but states regulate drug substitutions. Most states that allow interchangeable substitution require that pharmacies notify the prescriber within a relatively short time after a biologic-to-biosimilar switch.



What if I Don't Want to Switch?

Many health care providers are unlikely to switch patients who are doing well on a biologic. But if a biologic becomes less effective, your doctor might try a biosimilar. Or your insurance company might stop covering a biologic you take or require you try a biosimilar first. Payers have so far been slow to add biosimilars to their list of approved drugs, however. Check with your provider and insurance company to find out whether it covers your biologic or will require an alternative.



Are Biosimilars Safe for Kids?

Studies of biosimilars in kids are limited. Most biologic research has been done in adults, with some results extrapolated to children. And although a drug may be approved for both children and adults, it might not be appropriate for all the same conditions in kids as in adults. It may also be used off-label to treat other pediatric conditions. For example, infliximab (*Remicade*) biosimilars approved to treat inflammatory bowel disease in children 6 and older may be used off-label to treat juvenile idiopathic arthritis (JIA).

In existing pediatric studies, children seem to do as well on biosimilars as on the reference biologic. German researchers recently looked at the safety and effectiveness of two etanercept (*Enbrel*) biosimilars, *Benepali* and *Erelzi*, in nearly 400 children with JIA. Some started treatment with a biosimilar, some with *Enbrel* and a few switched from *Enbrel* to a biosimilar during the trial. (*Enbrel* biosimilars are available in Europe but won't be in the U.S. until the end of the decade.) The biologic and biosimilar groups both showed reduced disease activity or remission and about the same number and types of side effects.



What Are Unbranded Biologics?

Unbranded biologics are not biosimilars. They are originator biologics without the brand name on the packaging and label. Think of them as the generic form of biologics.

Are Biosimilars Safe During Pregnancy?

Most data about the safety of biosimilars in pregnancy and breastfeeding is extrapolated from studies of biologics. In one analysis of just 18 pregnancies where a biosimilar was used, 11 pregnant people stopped the drug in the second trimester — a decision made with their doctors. (The American College of Rheumatology suggests that certain biologics are safe through the second trimester.) Health record data showed no birth defects or other problems with a biosimilar; however, stopping the drug early was associated with disease flares, both before and after giving birth.

WHAT ARE PEOPLE SAYING?



What Do Doctors Say?

Some doctors have embraced biosimilars; others aren't completely convinced. Many have years of experience with biologics but far less with biosimilars, especially given the slow rollout in the U.S. Physician surveys in 2016 reported that only about half of doctors, including dermatologists and rheumatologists, trusted biosimilars. The numbers have improved since then, but there are lingering doubts, especially about the validity of extrapolation and the safety of biologic-to-biosimilar switching at pharmacies. Some dermatologists and rheumatologists, in particular, say they would prefer to prescribe a biologic over a biosimilar.

A lot of recent research is devoted to understanding barriers to biosimilar uptake. The general consensus is that many health care providers don't receive reliable regulatory and scientific information about biosimilar drugs. For example, some may not be aware that biologics themselves aren't identical; biologics from the same manufacturer are likely to differ slightly between batches or even within a single batch due to the inherent unpredictability of living organisms. Biosimilars have been successful in other countries in part because of widely available educational programs for physicians and patients.



Foods to Avoid with Biologics and Biosimilars

Some foods that are fine for healthy people may increase the chance of infection in those with weakened immune systems, including:

- Raw fish (as in sushi)
- Raw eggs and products that contain them
- Raw milk and raw cheeses

What Do Patients Say?

Patients also have concerns. They especially worry about being forced to switch to a biosimilar — or having a pharmacist switch them — when they're doing well on a biologic. These concerns are understandable, particularly if:

- Patients don't know how biosimilars work or are approved.
- Their doctor hasn't talked to them about biosimilars as a treatment option.
- Biosimilars aren't available on their formulary or offer no real cost savings to the patient over biologics.

Patient concerns and voices must be heard and respected. Having up-to-date, accurate and understandable health information is also critical. Yet some studies show that, while patients are generally satisfied and have positive outcomes when they switch to a biosimilar, they still have questions, even after discussions with health care providers. The goal of this book is to tackle common questions about biosimilars and provide answers you can refer back to so you can make the medical decisions that are right for you. Learn more at [arthritis.org/biologics](https://www.arthritis.org/biologics).



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