Thank you for opening this e-book on biologics. Biosimilars are biologic medicines that are highly similar to the original biologic medicine, sometimes we refer to this as the “name brand”. For the purposes of this e-book we will refer to them as originator biologics. Our hope is to provide enough information for you to make informed, educated decisions about the use of biologic drugs in your treatment plan.

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Patients Rising University is the education and empowerment arm of Patients Rising. Our goal is to give patients and caregivers the information they need (never to be confused with medical advice, ever) to have greater success in their pursuit of good healthcare. We believe that can be achieved by increasing knowledge and improving communication between patients, providers, insurers, legislators—anyone playing a role in healthcare. We don’t claim to be experts on the topics we write about, which is why we gather the best quality information from resources that are. You’re welcome to visit the Patients Rising University to explore the content that is posted there.
What Are Biologics?

Biologic drugs (“biologics”) come from living sources such as humans, animals, or microorganisms (bacteria and viruses). These relatively large, complex molecules or combinations of molecules are made using processes that are difficult to precisely replicate from one product manufacturer to the next. Non-biologic drugs (“drugs”), on the other hand, are small molecules that are generally less complex and can be more readily synthesized and replicated by various manufacturers.

Vaccines are biologics developed in live attenuated or inactivated viruses. Insulin products are biologics that are developed by adding human DNA to a common bacterium, which in turn produces a “recombinant protein” of human insulin. Other biologics include monoclonal antibodies, gene therapies, tissues, genes, allergens, cells, and blood components.¹

What Are Biosimilars?

It is tempting to say that biosimilars are to originator biologics as generics are to branded drugs, but that is too simplistic. A generic drug has the same active ingredient as the branded drug it copies, as well as the same strength, dose, and route of administration (oral, sublingual, intravenous, etc.). A generic drug is also bioequivalent to the branded drug it copies, meaning releases the active ingredient at the same amount and same rate in the body. Biologics cannot be copied in the same way as non-biologic drugs. Instead, biosimilars are biologics that are “highly similar” in structure and function to the original biologic, also referred to as the “reference drug.” A biosimilar also has no clinically meaningful differences in safety and efficacy compared to the reference drug. The precise molecular structure and function may have minor differences, but the safety and efficacy have no meaningful differences, which biosimilar manufacturers confirm by conducting clinical trials.

Are Biologics Commonly Prescribed?

Biologic use is not yet widespread in the U.S. While a 2019 Forbes article stated that they represent only 2 percent of all the prescriptions written in the U.S., biologic use is gradually increasing. Since 2014, an increasing percentage of drugs that are being developed are biologics.
Why You Should Care About Originator Biologics and Biosimilars

Biologics target specific proteins that are known to play a role in various inflammatory conditions triggered by abnormal immune responses, such as autoimmune diseases, anemia, chronic migraine, hepatitis B, hemophilia, rheumatoid arthritis, inflammatory bowel diseases and others. Biological drugs can play other important roles in the body such as helping to regulate blood sugar levels (insulins) or bone growth and even helping attack different cancers. They differ from the more common, non-biologic drugs in many ways that impact their manufacturing cost, how they are produced, administered, and work in patients. But rather than go that deep, we’re going to focus on the information about biologics, both originator and biosimilars, that will help you make informed decisions about your treatments.

A Note on Using the Terms “Biologic” and “Biosimilar”

Biosimilars are biologic drugs. They go through the biomanufacturing process but vary in some ways from the originator biologic that they are biosimilar to (the “reference product”). As such they are subject to similar side effects, storage, and administration parameters.
Compared to the traditional chemically synthesized drugs of which most of us are familiar, biologics are larger, more complex molecules that require some component from a living organism in order to be made.

Biologics are also more targeted than non-biologic drug treatments. For example, certain drugs for rheumatoid arthritis affect multiple parts of the patient’s immune system. Biologic drugs for rheumatoid arthritis, in contrast, block a very specific receptor on a very specific immune molecule. By narrowing in on a precise target, certain side effects may be avoided (which is not to say biologics don’t have side effects).

Because of the nature of biomanufacturing and the use of living cells, biologics tend to be more sensitive to heat and light and may need to be refrigerated. Often, they cannot be taken by mouth and must be given by injection or by intravenous infusion (IV).)

Each biologic may act differently in your body, based on the condition they target. Being on any one biologic does not mean your experience with another biologic will be the same. Biologics have different purposes, designs, molecular size, and methods of administration.

### How Do You Know If A Drug Is A Biologic?

Fortunately, the way drugs are named tells you something about them.

<table>
<thead>
<tr>
<th>Drug name ends in</th>
<th>Then it is a ...</th>
<th>Example ...</th>
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<tr>
<td>MAB</td>
<td>Monoclonal antibody (a biologic)</td>
<td>Denosumab</td>
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<tr>
<td>MIB</td>
<td>Small molecule protease or proteasome inhibitor</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>NIB</td>
<td>Small molecule kinase inhibitor</td>
<td>Alectinib</td>
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Of course, the best way to know if a drug is an originator biologic or a biosimilar or neither is to ask your doctor or pharmacist.
Potential Side Effects

Each biologic, including biosimilars, comes with its own potential for side effects. When considering whether or not a biologic is right for you, you can look up the possible side effects by doing an online search for “drug name + side effects.”

When you’ve done that search, you’ll have a few options of what to look at. Skip past the inevitable ads to what will likely be a dedicated website for the medication. When visiting such a site, look for “Patient Information” or, if you have more advanced medical/scientific knowledge, you can try “Prescribing Information.”

If you keep going past the dedicated website you will probably find other sources of information like MayoClinic.org or Drugs.com. If you want to limit your search to nonprofits, you can type your search like this: “drug name + side effects + org.” Likewise, if you want only federal sources of information like the U.S. Food and Drug Administration (FDA) or the National Institutes of Health (NIH), you can type “drug name + side effects + gov (or “FDA” or “NIH”)."

Just like potential side effects differ for each drug, they also differ among the people who use them. There is no substitute for speaking with your doctor about the risks and benefits of starting a new treatment.

Conditions Treated with Biologics

Biologic therapies have been developed to treat the following conditions:6
• Ankylosing Spondylitis
• Autoimmune diseases
• Breast Cancer
• Colon Cancer
• Crohn’s Disease
• Cystic Fibrosis
• Diabetes
• Diabetic Retinopathy
• Forms of Leukemia and Lymphoma
• Gastric Cancer
• Hemophilia
• Infertility
• Multiple Sclerosis
• Osteoporosis
• Sickle Cell Disease

If you are unsure if your medical condition has a biologic treatment option, ask your doctor.
How Biologics Are Administered

While prescription and over the counter drugs can be taken orally, biologics are often taken in the form of an injection or an infusion into a vein. If swallowed, most biologics would be broken down in the stomach and intestine before they could be absorbed into the bloodstream of the body. They are proteins that are unstable at room temperature—they cannot sit on pharmacy shelves like most non-biologic drugs.

The frequency of administration may depend on the type of biologic or the condition that they treat. Some biologics are given only once, while others must be administered periodically (e.g., once every 3 months), and yet others must be given daily. For most conditions, you will probably have to get the medication administered at your doctor’s office, an infusion center, or hospital. Some biologics can be self-administered at home. These are usually ones like insulin or hormone replacements that have to be taken every day.

How Biologics Are Made

Biologics are created through a process called biomanufacturing. In contrast, most non-biologic drugs are made through chemical synthesis and do not require living tissue.

Because biomanufacturing requires the handling and processing of living cells, it is a longer, more complex, and more expensive process than most drugs. To put it simply, the multistep biomanufacturing process uses genetics to create a unique cell line that ultimately produces the active ingredient of the biologic.

Safety During Pregnancy or Breast Feeding

Just like other discussions of risks and benefits, this is best done with your doctor. The risk of starting a biologic treatment may also be different than stopping a biologic treatment if you are already on one. So, if you become pregnant, or plan to, you should make a plan with your prescribing physician on how to proceed.
The FDA has approved biosimilar medications to treat conditions such as cancer, Crohn’s disease, colitis, rheumatoid arthritis, psoriasis, and more.

To reiterate: a biosimilar is a biologic that is highly similar to, and has no clinically meaningful differences from, another biologic that’s already approved by the FDA (known as the originator biologic or reference product). Biosimilars are made with the same types of natural sources as the original medication they were compared to; they are given the same way, have the same strength and dosage, and have the same potential side effects. A biosimilar provides the same treatment benefits as the originator biologic.

**Biosimilars Are Safe and Effective**

Biosimilars are as safe and effective as the originator biologic; both are rigorously and thoroughly evaluated by the FDA before approval.

Before approving a biosimilar, FDA experts must conclude it is highly similar to the reference product and that it has no clinically meaningful differences from the reference product. This means you can expect the same safety and effectiveness from the biosimilar over the course of treatment as you would from the reference product. This thorough evaluation helps to ensure that all biosimilar products are as safe and effective as their reference products and meet the FDA’s high standards for approval.

In addition, the FDA closely regulates the manufacturing of all biologics, including biosimilars. The same quality manufacturing standards that apply to originator biologics also apply to biosimilars. It must be manufactured in accordance with Current Good Manufacturing Practice requirements, which cover methods, facilities, and controls for the manufacturing, processing, packaging, or holding of a drug product. This helps to prevent manufacturing mistakes or unacceptable impurities and to ensure consistent product quality.8
Safety and Efficacy of Biosimilars

*The following information reproduced from FDA*

Biosimilars are safe and effective medications for treating many illnesses such as chronic skin and bowel diseases (like psoriasis, irritable bowel syndrome, Crohn’s disease and colitis), arthritis, kidney conditions, and cancer.

Biosimilars are FDA-approved biologic medications that are compared to another medication—the originator biologic or reference product.

Biologic medications are generally made from natural sources and developed using advanced science.

### Same Expected Benefits and Risks

Compared with their reference product, biosimilars:

- Are made with the same types of natural sources
- Are given the same way
- Provide the same treatment benefits
- Have the same potential side effects
- Have the same strength and dosage

### Improving Access and Earlier Treatment

Biosimilars may provide patients with more access to important treatments:

- More treatment options
- Earlier treatment with a biologic because of lower cost
- More competition in the healthcare market
- Lower costs

### Safe and Effective

FDA makes sure biosimilars are as safe and effective as the originator biologic by:

- Approving biosimilars after a careful review of data, studies, and tests
- Monitoring safety and effectiveness after approval
- Checking for medication quality during production
- Reviewing patient safety reports made to FDA
Interchangeable biosimilar products can be automatically substituted for the reference product by a pharmacist without physician intervention. Developers have to apply for an “interchangeable” designation. Currently, there is no interchangeable biosimilar in the U.S. as of this printing.

Generic drugs do not face substitution or interchangeability challenges as those are built into the FDA approval process, not as a separate step; in fact, that is what allows generic drugs to gain their share in the market. Generics are small molecules that are manufactured using a chemical reaction, while biosimilars are complex large molecule proteins that are manufactured using living cell systems.

Guidance from FDA

The FDA has released a guidance document that can assist manufacturers through the process of demonstrating interchangeability\(^1\) in support of their marketing application for an interchangeable biosimilar product. For interchangeability designation, the biosimilar product is expected to produce the same result as the reference product in any given patient. Additionally, if a biologic has to be administered to a patient more than once, the manufacturer has to provide the FDA with additional data to show that switching between the reference product and the biosimilar does not cause any safety concerns or reduce efficacy.

In order to provide this evidence, biosimilar manufacturers are generally expected to conduct additional prospective clinical studies, which would require investment of resources. The FDA will generally not accept post-marketing data on the use of a biosimilar in place of a switching study. We should note there is some flexibility built into the guidance that allows manufacturers to justify that data from a prospective switching study is not needed. However, their preference is data from a well-designed prospective study of at least three controlled switches in support of the desired interchangeability designation. Alternating between the reference product and its biosimilar, especially for treatments that have a long duration, may be associated with risks such as an immune reaction or reduced efficacy, which the biosimilar manufacturer needs to evaluate.
Clinical Evidence

One such study conducted in the U.S. compared the effect of switching patients with moderate-to-severe chronic plaque psoriasis\textsuperscript{11} between the reference drug Humira (adalimumab) and its biosimilar BI 695501 with patients treated continuously with Humira. In addition to pharmacokinetics of the drugs (how well the drug distributes in the body), the trial compared the safety, immunogenicity, and efficacy profiles in the two patient populations. The study is reported as closed as of October 2019, and there have not been reports of any other switching studies in 2019.

Substitution versus Interchangeability

An explanation for why manufacturers may not be in a rush to conduct switching studies is that therapeutic interchange of biologicals in hospitals is often allowed by pharmacy and therapeutics (P&T) committees.\textsuperscript{12} Therefore, in a hospital system, the P&T committee may decide on the formulary inclusion of a biosimilar, irrespective of an interchangeability designation. Physicians always have the ability to prescribe whatever medication they think is appropriate for their patient, irrespective of whether it is designated by the FDA as an interchangeable biosimilar. Interchangeability only applies to pharmacist-initiated switches.
State Laws for Switching/Interchangeability

While the FDA provides guidance for developing an interchangeable biosimilar, the substitution decision will be driven by state pharmacy laws once an interchangeable biosimilar is available. In preparation for such a product, 49 states and Puerto Rico have passed laws that allow a pharmacist to dispense an interchangeable biosimilar product.\textsuperscript{13} Automatic substitution will be allowed only if:

- The biosimilar has been approved by the FDA as interchangeable
- The prescriber has not indicated that substitution is prohibited

Depending on the states, a pharmacist may be required to inform the prescriber and the patient of the switching within a specified time after dispensing the biosimilar and also maintain a record of the switch.

South Carolina and West Virginia, however, have a different approach. Pharmacists in South Carolina can substitute with a biosimilar if it is interchangeable or if the pharmacist deems it to be therapeutically equivalent to the reference product prescribed by the physician.

In West Virginia, pharmacists have been instructed to substitute with the less expensive interchangeable biosimilar unless the pharmacist is of the opinion that it will not be suitable for the patient.

The European Experience

“Interchangeable” does not have the same meaning in the EU. Interchangeability in the EU, and in the cited reference, is used to mean a prescriber-led decision to switch a patient’s medication. It does not equate to pharmacy substitution the way is does in the U.S. In European nations, use of a biosimilar instead of a reference is encouraged in treatment-naïve patients. Switching from a reference to a biosimilar is usually encouraged under close supervision of a clinician, and a pharmacist-level substitution may be an exception. However, unlike in the U.S., European health authorities do not require an additional switching study.\textsuperscript{14} Post-marketing data from Europe have provided sufficient evidence to show that biosimilar switching does not affect safety or efficacy.
In the U.S., biosimilars are beginning to see widespread use, as with Europe, where biosimilar drugs have been available since 2006. The 2010 Affordable Care Act (ACA) addressed this issue via the Biologics Price Competition and Innovation Act (BPCIA)—a regulatory allowance to let manufacturers of follow-on products to rely in part on the clinical data of the brand name reference product to which it is “similar”. The expectation was that this would reduce product development costs and spur market competition, as was seen in the world of generic products. Increased competition in turn helps bring down prices and improves patient access. A decade later, we are beginning to see significant uptick in the use of biosimilars in the U.S.—as of July 2020, 28 biosimilars have been approved in the U.S.
Technology Challenges with the Biomanufacturing

Unlike small molecule drugs that are manufactured by chemical reactions, biosimilars are “biologics”—complex large molecules that are bio-manufactured in living cells such as microorganisms, plant cells, or animal cells. All biologics, which may be a therapeutic protein, monoclonal antibody, or vaccine, can have batch-to-batch variations in the product. The FDA has set standards to ensure that these variations remain within limits to ensure clinical efficacy; further variations occur with biomanufacturing of any product, including the reference product. Biosimilar manufacturers therefore need stringent process-control strategies to ensure their product is as clinically effective as the reference biologic.

Commonly Recognized Barriers

Multiple aspects relevant to biosimilar manufacturing, patents, drug administration, restrictive contracts, and certain reimbursement policies have posed challenges to the widespread use of biosimilar products.

Technology Challenges with the Biomanufacturing

Unlike small molecule drugs that are manufactured by chemical reactions, biosimilars are “biologics”—complex large molecules that are bio-manufactured in living cells such as microorganisms, plant cells, or animal cells. All biologics, which may be a therapeutic protein, monoclonal antibody, or vaccine, can have batch-to-batch variations in the product. The FDA has set standards to ensure that these variations remain within limits to ensure clinical efficacy; further variations occur with biomanufacturing of any product, including the reference product. Biosimilar manufacturers therefore need stringent process-control strategies to ensure their product is as clinically effective as the reference biologic.

Drug Administration

Biologic and biosimilar products are proteins and often need to be injected or infused in a clinic, which makes drug administration less convenient and adds to the time spent on treatment and the cost of care. There are also a few biologics and biosimilars that patients can self-administer using an auto-injector.

Patents

The complexity of a biological product has led manufacturers of reference biologics to often obtain far more patents than an average small molecule drug manufacturer. Restrictions imposed by patents further delay biosimilar market entry, as has been seen with the anti-inflammatory drug adalimumab (Humira). Adalimumab has broad indications for the treatment of arthritis, plaque psoriasis, ankylosing spondylitis, and Crohn’s disease, among others. Five biosimilar adalimumab products have so far received FDA approval, but patent agreements with the reference product manufacturer have pushed product launch to 2023.16,17

It has also led to several lawsuits filed by worker unions and health plans alleging anticompetitive practices. To protect their original biologic patents, reference product manufacturers have filed lawsuits against biosimilar manufacturers,18 The large number of patents, some of which extend far beyond the expiration of the original drug patent, adds to legal expenses and has potential to delay product launches.”
Physician Reluctance

Physicians’ skepticism toward biosimilar products remains. A survey among rheumatologists, conducted by the healthcare services company Cardinal Health, found:19

- While a majority were familiar and comfortable with prescribing biosimilars, only 11% said they were likely to replace the reference product with a biosimilar in a patient who was responding to the reference biologic
- The physicians indicated that they did not believe biosimilars present a significant cost benefit
- 38% of respondents were concerned about biosimilar efficacy
- 45% were concerned with interchangeability and extrapolation, i.e., using a biosimilar for indications that the reference product was approved for but the biosimilar was not clinically tested for

It is important to note that a similar trend in the small molecule generics market in the 1980s faded away with increased public awareness of generics. Biosimilar manufacturers can take a similar approach and educate physicians and other health care providers on the science behind biosimilars to increase their trust in these products.

Payers, PBMs, and Formularies

Payers and Pharmacy Benefit Managers (PBMs) are the gatekeepers for what is included on a formulary, which is the list of drugs covered by a payer. Biosimilar products often struggle to replace the reference biologic on these formularies, primarily due to pre-negotiated contracts between payers and drug manufacturers called exclusivity contracts. Additionally, the multi-payer health care system in the U.S.—both government and private—adds to the lack of standardized policies around formulary decisions. There is opportunity to educate payers and PBMs on the concept of biosimilarity.
Paving the Way for a Robust U.S. Biosimilars Market

A multi-pronged approach will be needed for expansion of the U.S. biosimilar and interchangeable market and for improved patient access to these drugs.

FDA

On its end, the FDA released a Biosimilars Action Plan in the summer of 2018 to ensure continued innovation and competition in the biologics space, including:

- Developing and implementing new review tools for an efficient FDA review process and keeping the public abreast of progress
- Creating information resources and development tools for biosimilar manufacturers to ease their biosimilar drug development process
- Exploring the potential for data-sharing agreements with drug regulators in other nations to gain access to non-U.S.-licensed comparator products in studies that can help biosimilar applications
- Establishing an independent Office of Therapeutic Biologics and Biosimilars to coordinate and support biosimilar development
- Continue educating health care professionals on biosimilars and interchangeable biologics
- Engage in a public dialogue to gain feedback on additional policy steps that the FDA could consider for enhancing the biosimilar program

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Policy Proposals to Bolster the Biosimilars Market

Many stakeholders in the biosimilar space believe that creating physician and patient incentives to use the lower cost biosimilars would help boost the biosimilar market in the US.

The Bolstering Innovative Options to Save Immediately on Medicines (BIOSIM) Act (H.R.4455) was introduced in the House in September 2019 to provide for a temporary increase in Medicare Part B reimbursement of certain biosimilar products. Sen. Cornyn (R-TX) and Sen. Bennet (D-CO) introduced S 4134, Increasing Access to Biosimilars Act of 2020, a bill that aims to lower health care costs and increase access to biosimilars by instructing CMS to develop a shared savings model for biosimilars.

In an attempt to incentivize patients to use biosimilar products, a bipartisan bill was introduced in the House in October 2019 that proposes to eliminate Medicare Part B copayment when a patient takes a biosimilar product instead of the reference biologic. Acting to Cancel Copays and Ensure Substantial Savings for Biosimilars (ACCESS) Act (H.R.4597) was introduced in the House in September 2019 on the heels of a letter submitted by about 20 groups to HHS Secretary Alex Azar urging CMS to consider reducing or eliminating patient cost-sharing for biosimilars under Medicare Part B.

ACA and the Biosimilar Approval Pathway

If the Supreme Court overturns the ACA in its entirety, it will unravel the progress to date with biosimilar products because the BPCIA is embedded within the ACA. The FDA would subsequently lose its authority over the biosimilar approval pathway and this could disincentivize biosimilar manufacturers/developers to continue making these potentially cost-saving products.

Addressing the adverse impact of revoking the ACA, the Association of Accessible Medicines filed a brief in support of biosimilar development and urging the Supreme Court to sever the BPCIA from the ACA. “The BPCIA is exactly the type of legislation that should not be declared invalid based on a constitutional challenge to another part of the same public law. The BPCIA stands on its own and serves an important public purpose that is entirely disconnected from the insurance-related provisions of the ACA that are challenged here,” the brief states.

Physician Education

As mentioned earlier, physician skepticism with biosimilar use can be overcome by educating them on the structural similarity between a biosimilar and the reference biologic and assuring them that the biosimilar has equivalent safety and efficacy as the reference product. In a statement released in 2018, the American Society of Clinical Oncology (ASCO) recognized the important role of educating its oncologists on biosimilars and developing practice guidelines on how biosimilars are prescribed, administered, and dispensed. The American College of Rheumatology published a white paper geared toward rheumatology professionals that explains the science behind biosimilars, specific terms such as substitution and interchangeability, as well as the economics that impact patient access to these products.
This table imported from FDA

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<th>Biosimilar Name</th>
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<th>Treatment for</th>
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<tr>
<td>Udenyca (pegfilgrastim-cbqv)</td>
<td>Nov 2018</td>
<td>Neulasta (pegfilgrastim)</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Zarfio (Filgrastim-sndz)</td>
<td>Mar 2015</td>
<td>Neupogen (filgrastim)</td>
<td>Reduced white blood cell count</td>
</tr>
<tr>
<td>Ziekttenzo (pegfilgrastim-bmez)</td>
<td>Nov 2019</td>
<td>Neluasta (pegfilgrastim)</td>
<td>Non-myeloid malignancies receiving myelosuppressive anti-cancer drugs</td>
</tr>
<tr>
<td>Zirabez (bevacizumab-bvzr)</td>
<td>Jun 2019</td>
<td>Avastin (bevacizumab)</td>
<td>Multiple different types of cancer</td>
</tr>
</tbody>
</table>
Notes

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