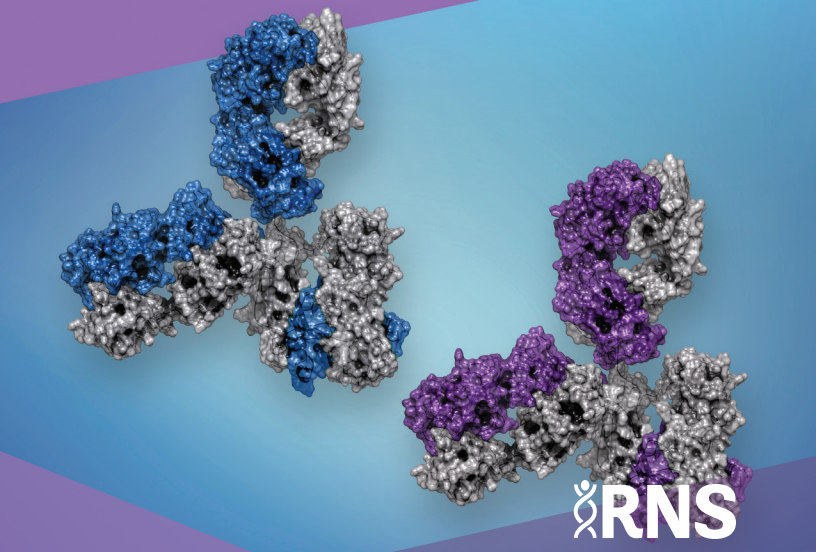
Rheumatology Nurses Society
Professional Education Series

HANDLING THE
HARD QUESTIONS:

What Our Patients Are Asking Us About
BIOSIMILARS



The Purpose of This Document

Each week, rheumatology nurses and advanced practice providers (nurse practitioners and physician assistants) field challenging questions from their patients with rheumatic diseases about the coming wave of biosimilars, and they need to be able to properly and effectively communicate appropriate responses. This pocket guide includes a brief summary of evidence surrounding some of the most common—and challenging—questions that patients with rheumatic disease are asking about biosimilars. We hope you find this guide useful for your professional development.

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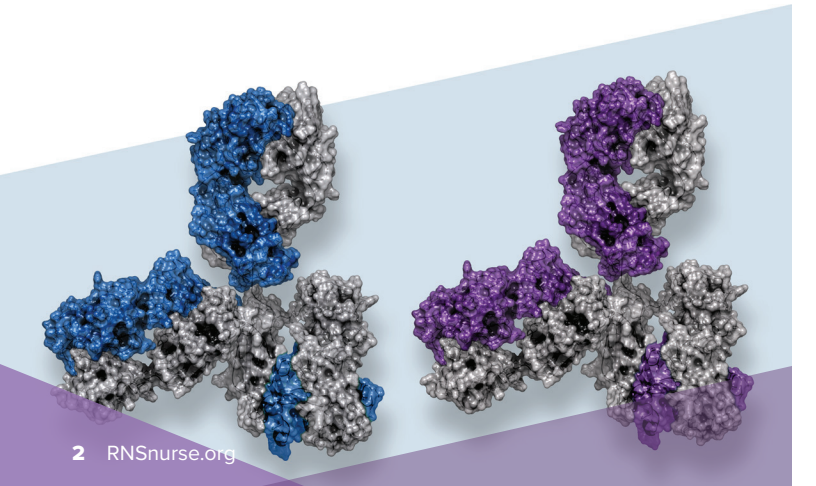
What is a biosimilar?

A biosimilar is a biologic agent that is highly similar to a previously-approved, brand-name biologic disease modifying antirheumatic drug (DMARD).

Over the last several decades, scientific advances have led to the development of new treatment approaches for patients with systemic, immune-mediated rheumatic diseases such as rheumatoid arthritis and psoriatic arthritis. Many of these new medications are biologic agents. Biologics are typically large, complex molecules that are derived from the extracted and purified DNA of living organisms such as plants, animals, or micro-organisms. As such, they are markedly different from non-biologic drugs that you might see at a traditional pharmacy (i.e., an oral antibiotic or a pill to lower blood pressure or cholesterol), which are typically synthesized from specific chemical formulas.[1]



Numerous biologics, including those used for the treatment of rheumatic disease, have received U.S. Food and Drug Administration (FDA) approval to help reduce or block the effects of the inflammatory process in the body.[2] When any new drug is approved—biologic or otherwise—the manufacturer receives a patent that protects the drug's exclusivity for 20 years from the invention of the drug (the amount of time it is approved and therefore available to the public will typically be far shorter). When the original (sometimes called "reference" or "originator") medication's patent protection expires, other drug companies can begin to make and market their own version of that drug.[3]

In the case of biologic agents, when a manufacturer makes a version of an already approved reference drug, it is called a "biosimilar." Unlike traditional drugs made from chemical formulas, manufacturers of biosimilars don't have the precise manufacturing recipe for a reference drug; rather, they reverse-engineer the original biologic to determine how to make it.[4] The end product, therefore, is not an exact replica, but highly similar.

In order to file for FDA approval of a biosimilar, manufacturers must demonstrate, through extensive evaluation and testing, that their proposed biologic product is *highly similar and has no clinically meaningful differences from an existing, FDA-approved reference product*. A biosimilar is **highly similar** if its structure and function is similar to the reference biologic. It has **no clinical meaningful differences** if studies show comparable efficacy and safety. After biosimilars receive FDA approval and

are marketed, their safety is tracked and monitored through ongoing pharmacovigilance.[1]

Often, patients will ask if a biosimilar is akin to a generic drug. The short answer is no. While both biosimilars and generics are indeed later versions of brand name drugs, there are important differences. Namely, biosimilar manufacturers must show their agent is highly similar to the reference drug in clinical trials and that there are **no clinically meaningful** differences between the biosimilar and reference product in terms of safety or efficacy. In contrast, manufacturers of generic drugs must only show that the active ingredients of the generic are the same as the brand name drug and that there is overall bioequivalence.[1]

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How do biosimilars become approved by the FDA?

Although rigorous, the approval process for a biosimilar differs from that used for a reference biologic. Biosimilars typically seek FDA approval through something called an abbreviated licensure pathway. This pathway still ensures safety and efficacy of every biosimilar before it can be used in the clinical setting, but differs in breadth and duration from the pathway of an originator biologic.

A reference biologic must undergo extensive preclinical and clinical evaluation to show that it is safe and effective for each specific disease or condition for which the manufacturer is seeking FDA approval. When data confirm this, manufacturers file a biologics license application (BLA); if approved, the biologic can be marketed and sold for use.

In contrast, biosimilar manufacturers are not required to rigorously establish the safety and efficacy of their product in preclinical trials, as that has already presumably been done during trials of the reference biologic. Rather, they must demonstrate that their product is highly similar to, and has no clinically meaningful differences in safety, purity, and potency from, an existing FDA-approved reference product. The FDA becomes involved early in the review process, evaluating each biosimilar on a case-by-case basis to see what sort of data the manufacturer will be required to produce in order to demonstrate biosimilarity and file for an abbreviated or regular BLA.

When a biosimilar receives FDA approval, it may also be approved for indications other than those that were directly studied by the manufacturer. This is called extrapolation of indications—this means that the biosimilar may be approved for some or all of the reference product's indications if the manufacturer provides appropriate scientific justification.

Experts have expressed hope that the abbreviated licensure pathway will allow for potentially shorter and less expensive biosimilar development programs, all the while maintaining high approval standards.[1]

Another term that some patients may bring up is biobetters. While inspired by a reference biologic, biobetters are considered modified and upgraded versions of the originator biologic with improved safety, efficacy, and/or dosing regimens.[2] Whereas biosimilars must have similar active compounds to the reference product, biobetters are considered

to have structurally and/or functionally modified active compounds.[3] As such, biobetters are treated as if they are new biologic product and travel through the same research, development, and approval process as a reference product.[2] Additionally, biobetters are considered a novel product, so there are no limitations on when they can be developed or launched (i.e., they do not have to wait for reference product patent or exclusivity to expire as biosimilars do).[2] To date, there are no biobetters that have been approved for use by the FDA.

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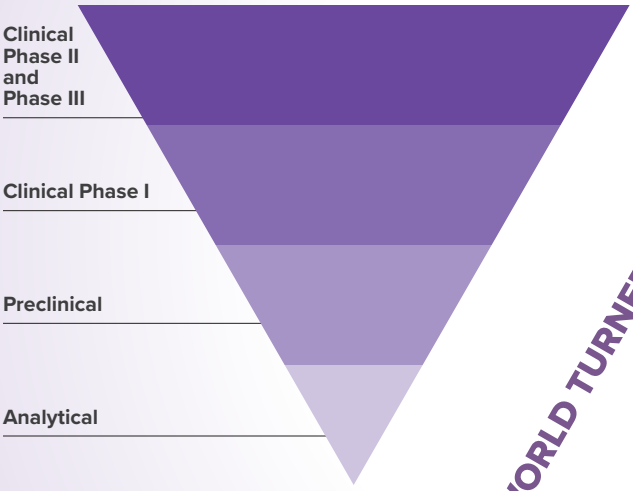
Table. The Difference Between Biologic and Biosimilar Approval Processes

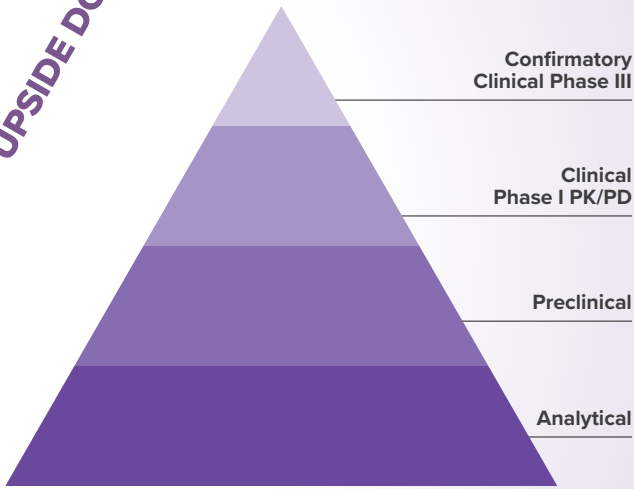
REFERENCE MEDICINE DEVELOPMENT

Main goal is to determine the clinical effect for each indication



THE WORLD TURNED

UPSIDE DOWN...



BIOSIMILAR DEVELOPMENT

Main goal is to establish similarity to the reference medicine

How long have biosimilars been around?

While biosimilars are relatively new in the United States, they have been available in other parts of the world for more than a decade. The European Medicines Agency has led the charge, approving the first biosimilar for use in the European Union in 2006. Since that time, more than 50 biosimilars have been approved for use in the European Union across various indications.[1]

In contrast, it wasn't until 2015 that the U.S. Food & Drug Administration (FDA) granted approval to the first biosimilar for use in the United States.[2]

Since then, however, acceleration has come quickly in the United States. There are 18 biosimilars approved for use in the United States (as of April 2019). Of those 18 approvals, 15 have come since 2017. To date, eight biosimilars have been approved for use in patients with rheumatic diseases.[3]

ORIGINATOR BIOLOGIC
Etanercept (Enbrel)
Adalimumab (Humira)
Infliximab (Remicade)
Adalimumab (Humira)
Infliximab (Remicade)
Adalimumab (Humira)
Etanercept (Enbrel)
Infliximab (Remicade)

Table. Rheumatology Biosimilars Approved for Use in the United States

BIOSIMILAR	APPROVAL DATE	INDICATION
Etanercept-ykro (Eticovo)	April 2019	RA, polyarticular JIA, PsA, AS, plaque psoriasis
Adalimumab-adaz (Hyrimoz)	October 2018	RA, juvenile RA, PsA, AS, plaque psoriasis, adult Crohn's disease, ulcerative colitis
Infliximab-qbtx (Ixifi)	December 2017	RA, PsA, AS, plaque psoriasis, adult/pediatric Crohn's disease, ulcerative colitis
Adalimumab-adbm (Cyltezo)	August 2017	RA, JIA, PsA, AS, plaque psoriasis,adult Crohn's disease, ulcerative colitis
Infliximab-abda (Renflexis)	May 2017	RA, PsA, AS, plaque psoriasis, adult/pediatric Crohn's disease, ulcerative colitis
Adalimumab-atto (Amjevita)	September 2016	RA, JIA, PsA, AS, plaque psoriasis, adult Crohn's disease, ulcerative colitis
Etanercept-szzs (Erelzi)	August 2016	RA, JIA, AS
Infliximab-dyyb (Inflectra)	April 2016	RA, PsA, AS, plaque psoriasis, adult/pediatric Crohn's disease, ulcerative colitis

RA = rheumatoid arthritis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; AS = ankylosing spondylitis

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Are there different safety concerns with a biosimilar compared to its reference biologic?

Not really.

Remember, a biosimilar is a *biological product that is highly similar and has no clinically meaningful differences from an existing FDA-approved reference product*. So, what does this mean?

1. **Highly similar**

   - Extensive analysis of the structure and function of both the proposed biosimilar and reference product
   - Comparable purity, chemical identity, and bioactivity

- Minor differences in clinically inactive components are OK
- Slight variations in lot-to-lot differences are OK

2. No clinically meaningful differences

- Human exposure/response and clinical immunogenicity studies show no clinically meaningful differences between proposed biosimilar and reference product in terms of safety, purity, and potency (i.e., safety and effectiveness)

One of the FDA's priorities during the biosimilar review process is to carefully evaluate any differences between the proposed biosimilar and the reference product to ensure the proposed biosimilar meets FDA standards. Furthermore, given that all biologics are manufactured from living organisms, slight lot-to-lot variations are expected.[1] In fact, biologics themselves typically go through small variations during their approved lifespan. One 2013 study showed that there were 37 approved manufacturing changes during the first 14 years of infliximab's approval, ranging from changes in raw material supplier to process improvements to the addition of new manufacturing sites, that likely caused slight variations in the subsequent production of infliximab. As such, some experts claim that any biologic a clinician administers to a patient today is not identical but rather highly comparable to the original biologic authorized by the FDA.[2]

One of the primary concerns about biosimilars is that there will be unique safety profiles compared to their reference product and therefore patients will be exposed to unanticipated adverse events.[3] Reassuringly, numerous studies have shown the overall safety, efficacy, and immunogenicity of reference biologics and their FDA-approved biosimilars to be comparable.[4]

The issue of extrapolation of indications has also been a source of unease. Extrapolation has allowed some biosimilars to be approved for use in some disease states without having been directly evaluated in that specific population.[3] Fortunately, emerging clinical and real-world data evaluating infliximab biosimilars vs. originator infliximab across a range of diseases indicate comparable safety and efficacy, supporting the strategy of regulated extrapolation of indications for biosimilars.[5]

Going forward, ongoing post-marketing surveillance to identify and report adverse events and new safety signals (pharmacovigilance) will remain central to biologic and biosimilar use.[3]

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How can there be more than one biosimilar for a specific biologic?

Credit the Biologics Price Competition and Innovation Act of 2009, which was enacted as part of the Affordable Care Act. This statute created an abbreviated pathway for the approval and licensure of biosimilar products.[1]

Manufacturers of innovator drugs typically file for patent protection for their product; this protection lasts for 20 years from the invention of the drug. There is usually a long research and development cycle for a new drug, potentially running down the patent protection period. Therefore, when an originator biologic receives FDA marketing approval, the product also receives 12-year marketing exclusivity and 4-year data exclusivity, both starting with the date of first licensure. These

exclusivities are provided in order to encourage research and development of these typically very complex and expensive products, especially if the patent is close to expiring.

This means a manufacturer may work on the development of a biosimilar at any time but cannot submit for FDA review until the 4-year data exclusivity window for the reference product has expired. Furthermore, even if the FDA reviews the biosimilar after the expiration of the 4-year data exclusivity period, that agent cannot be marketed until the 12-year marketing exclusivity and/or patent protection ends.[1,2]

Manufacturers of biosimilars don't have access to proprietary ingredients, manufacturing processes, and other trade secrets for the reference product; instead, they use the reference product to reverse engineer the biosimilar to be a highly similar version of the reference product.[3] As such, every manufacturer will use their own, slightly different approach when researching and developing a potential biosimilar product.

Unlike the generics market, first-to-market biosimilars do not receive an exclusivity period (the exception being if a biosimilar is approved as the first interchangeable agent, in which case market exclusivity can be up to 1 year).[1,2] As a result, there is no limit to the number of biosimilars under development and/or available for a specific reference biologic.[2]

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What's with the weird names of biosimilars?

In a nutshell, the names are designed to reduce confusion and make sure that providers and patients understand what they are prescribing or taking.

In anticipation of the approval of the initial wave of biosimilars, in 2015, the FDA issued draft guidance regarding the manner in which biologics and biosimilars should be named. This draft guidance was updated in 2017 and again in 2019. While there remains some debate over the details of the naming conventions, all parties agree that consistent naming standards are necessary in order to minimize confusion as new biologics and biosimilars become available for clinical use.

Originally, the originator (or reference) biologic product was assigned a non-proprietary proper name (a non-brand name, such as adalimumab, etanercept, or infliximab). When a biosimilar for the originator biologic received FDA approval, it was also assigned its own non-proprietary name, built upon the following two components:

- **The core name:** The naming component shared among an originator biologic and the biosimilar
- **A unique 4-letter suffix:** This suffix is empty of any meaning. It should not suggest anything specific, form a word itself, or be too similar to the suffixes of other products. It must also be void of any numbers or symbols. At least 3 of the 4 letters must be distinct from one another. This has led to funny-looking generic names such as adalimumab-adaz instead of adalimumab-PAIN or infliximab-CURE.

However, the picture is about to get more confusing.

With the 2017 draft guidance, the FDA suggested the *Core Name + Unique 4-letter Suffix* approach be used for each originator biologic as well as any related biologic or biosimilar. The guidance suggested that this be implemented not only for future products but retroactively for previously-approved biologics. Not surprisingly, there was substantial outcry over the burden of requiring retroactive changing of the names of existing products without the 4-letter suffix.[1]

Consequently, the FDA released new guidance in March 2019. According to this guidance, no name modifications would be required for previously approved biologics. However, the *Core Name + Unique 4-letter Suffix* approach will be used for all newly approved or licensed originator biologics and any related, biosimilar, or interchangeable products. It is hoped this new approach will reduce the risk of false perceptions amongst providers and patients that there is a difference in the safety and efficacy of biologics and biosimilars based on name alone.[2,3]

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Can my pharmacist switch my biologic with a biosimilar without telling me?

No, not at the current time.

Substitution is the practice that allows a pharmacist to replace one drug (e.g., a brand-name drug) with another comparable drug (e.g., a generic) without the involvement or approval of the prescribing provider. While this is permitted in some instances for non-biologics, it is not currently permissible for biologics, although that may change in the future.

Interchangeability is the term that would allow biosimilars to be potentially substituted by a pharmacist without clinician or patient knowledge. In order for a biosimilar to be deemed interchangeable with a biologic, the biosimilar must meet stringent requirements from the

FDA. According to non-binding published draft guidance, this includes additional manufacturer evaluation and testing beyond the biosimilar approval process such as the collection of post-marketing pharmacovigilance data and switching studies.

In the proposed guidance, these studies must show the following:

- The proposed biosimilar has demonstrated biosimilarity to the reference product
- The proposed biosimilar will produce the same clinical results in any given patient as the reference biologic
- There is no increased risk in terms of safety or decreased efficacy if the biosimilar is given more than once to an individual, either as a switch from or alternating with the reference biologic, compared with using the reference product without such alternation or switch.[1,2]

The pathway for biosimilar interchangeability has not yet been finalized. As such, none of the currently approved biosimilars in the United States have received FDA designation as interchangeable with their reference biologic. Therefore, pharmacists still need a new prescription from a prescriber before they can substitute one biologic for another.[2]

In anticipation of biosimilars being deemed interchangeable in the future, the American College of Rheumatology (ACR) has stated that *the ACR believes that only prescribing providers should be allowed to substitute a biosimilar for the reference*

biologic or to switch among biosimilars…and in jurisdiction where substitution by someone other than the prescribing provider is lawful, the prescribing provider and the patient should be notified immediately when a substitution is made.[3]

Furthermore, substitution rules are governed by state statutes, and most states currently allow prescribers to prevent automatic substitution by writing notes on the prescription, such as "dispense as written" or "brand medically necessary."[2]

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Why do I need to switch from a biologic that is working to a biosimilar?

It basically comes down to economics. While still a bit unclear, the use of biosimilars may be associated with cost savings, catching the attention of cost-conscious payors (insurance and pharmacy benefit managers) who may require providers to switch patients responding to a biologic to a related biosimilar no matter their current level of clinical response.

Biologic DMARDs (bDMARDs) have transformed outcomes for many individuals with rheumatic diseases; however, they are very expensive, especially in light of the need for their long-term and perhaps lifelong use. Biosimilars are seen as a way to encourage competition among manufacturers, potentially leading to downward pricing pressure

and increased patient access to life-altering medications.[1] For instance, a recent analysis found that the annual cost for the tumor necrosis factor inhibitor (TNFi) infliximab was more than $17,300. While the biosimilar infliximab-dyyb was still expensive at approximately $14,200 per year, it still cost about 18% less than its branded reference biologic.[2]

Insurance companies and pharmacy benefit managers (PBM) wield enormous power over which medications they will or won't cover on their formularies as well as which ones are "preferred." As an example, one major PBM (Express Scripts) no longer provides coverage for the reference biologic filgrastim, a drug used to treat a cancer-related side effect called neutropenia, only providing coverage for two of its biosimilars.[1] While this is not yet the case for any biosimilar in rheumatology, the potential is there in the future.

As payors make changes to their formularies, they may impose payor substitution requirements on their members. In this case, patients are told they must switch from a medication they are currently taking (e.g., a reference biologic) to another (e.g, a biosimilar) for reasons unrelated to a drug's safety, efficacy, or tolerability, despite the fact they may be doing well on their current medication.[3]

Here is the good news. Numerous studies have looked at patients who switched from an originator bDMARD to a biosimilar and compared their outcomes to patients who started and stayed on either an originator or its biosimilar. Outcomes in terms of safety, efficacy, and immunogenicity have been

comparable.[4] This should be reassuring to both providers and patients who may have concerns about switching from an originator bDMARD to a biosimilar.

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Will my out-of-pocket insurance costs go down on a biosimilar?

Hopefully, but it largely depends on your insurance plan as well as biosimilar pricing.

It is thought that biosimilars will drive competition and accrue cost savings for payers and providers. For instance, one recent analysis found that the incorporation of biosimilars in the United States will reduce direct spending on biologic therapy by 3% over a 10-year period, translating to an overall savings of $54 billion.[1]

That said, it is less clear if these estimated savings will trickle down to patients.

Most commercial insurance plans, as well as Medicare Part D, have some form of patient cost-sharing, which contributes to patient out-of-pocket

expenses. Cost-sharing may consist of deductibles, co-insurance, and/or co-pays; these will vary depending upon the type of insurance coverage. Co-insurance is typically a fixed percentage of a medication's list price, whereas a co-pay is a fixed amount.[2]

Most biologics are considered "specialty drugs," which places them on a specialty formulary tier. Such tiers are often subject to high co-insurance rates, typically around 20-35% of the listed drug cost.[1,3] One emerging strategy being used by manufacturers, commercial insurance companies, and PBMs includes placing a biosimilar in the preferred drug tier, which is often associated with a lower rate of co-insurance. This can lead to lower out-of-pocket costs for patients compared with medications in the specialty or non-preferred tiers.[4] Furthermore, patients enrolled in the self-administered Medicare Part D program may actually currently pay more for biosimilars compared with the reference biologic, as manufacturers don't need to provide discounts for biosimilars to offset gaps in drug coverage. However, this is set to change starting in 2020, when manufacturers will need to start providing discounts to close the coverage gap for biosimilars.[5,6]

Patient out-of-pocket costs will ultimately depend on biosimilar vs. reference biologic pricing, formulary tier placement, as well as insurance plan cost-sharing requirements. Given different cost-sharing structures, lower biosimilar pricing

will likely benefit individuals with insurance plans having a significant co-insurance component, while those with co-pays may not see significant savings.

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Why are so few of the approved biosimilars available for current use?

Approval does not necessarily equal commercial availability, primarily due to patent litigation.

Since 2016, seven biosimilars have been approved for use in the United States for patients with immune-mediated rheumatologic conditions. Despite these approvals, only two biosimilars have been launched in the commercial U.S. market—infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis).

Several manufacturers of originator biologics have staved off biosimilar competition with patent protection lawsuits. For instance, AbbVie, the manufacturer of adalimumab (Humira), has successfully blocked three adalimumab biosimilars from entering the U.S. market until 2023.[1]

Similarly, the manufacturers of etanercept (Enbrel) and the etanercept biosimilar (etanercept-szzs, Erelzi) are embroiled in a lawsuit to determine the duration of patent protection coverage and expiration dates in the United States.[2]

Legal challenges appear to be a growing trend in the United States as manufacturers have tended to file significantly more patents on their products in the United States compared with other geographic regions. For example, there are 57 patents covering etanercept in the United States compared with 20 patents in Europe.[3]

Intra-manufacturer competition appears to be playing a role as well. For instance, after FDA approval of infliximab-qbtx (Ixifi), Pfizer announced it would not launch the biosimilar in the United States as it already has another infliximab biosimilar (infliximab-dyyb, Inflectra) on the market.[4] That drug was acquired by Pfizer in a 2015 takeover of Hospira.

Beyond patent litigation delaying product launch, several other potential barriers to biosimilars gaining widespread traction have been proposed, such as the following:[5-7]

- None of the currently approved biosimilars in the United States have been granted interchangeability status, so automatic substitution at the pharmacy level is not an option

- Biosimilars are still relatively new, so provider education, familiarity, and acceptance is still limited
- While biosimilars are somewhat less expensive to manufacture than reference biologics, they are still expensive, limiting the pricing discounts that manufacturers can offer. These discounts have not been substantial enough to significantly shift demand away from the branded reference biologic.
- Until 2018, biosimilars of a common reference biologic all carried the same billing code, limiting pricing variability. Now, each biosimilar has an individual billing code, allowing for future pricing competition.

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Table. Approval vs. Availability of Rheumatology Biosimilars in the United States[1,2,4]

BIOSIMILAR	MANUFACTURER	APPROVAL DATE
Infliximab-dyyb (Inflectra)	Pfizer	April 2016
Etanercept-szzs (Erelzi)	Sandoz	August 2016
Adalimumab-atto (Amjevita)	Amgen	September 2016
Infliximab-abda (Renflexis)	Merck & Samsung Bioepis	May 2017
Adalimumab-adbm (Cyltezo)	Boehringer Ingelheim	May 2017
Infliximab-qbtx (Ixifi)	Pfizer	December 2017
Adalimumab-adaz (Hyrimoz)	Sandoz	October 2018
Etanercept-ykro (Eticovo)	Samsung Bioepis	April 2019

COMMERCIALLY AVAILABLE IN THE U.S.	LIKELY DATE OF AVAILABILITY
Yes	Already available
No	In patent litigation with decision expected in 2019
No	2023
Yes	Already available
No	Unknown, still in patent litigation
No	Not planning to be launched in the U.S.
No	2023
Unknown	TBD

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