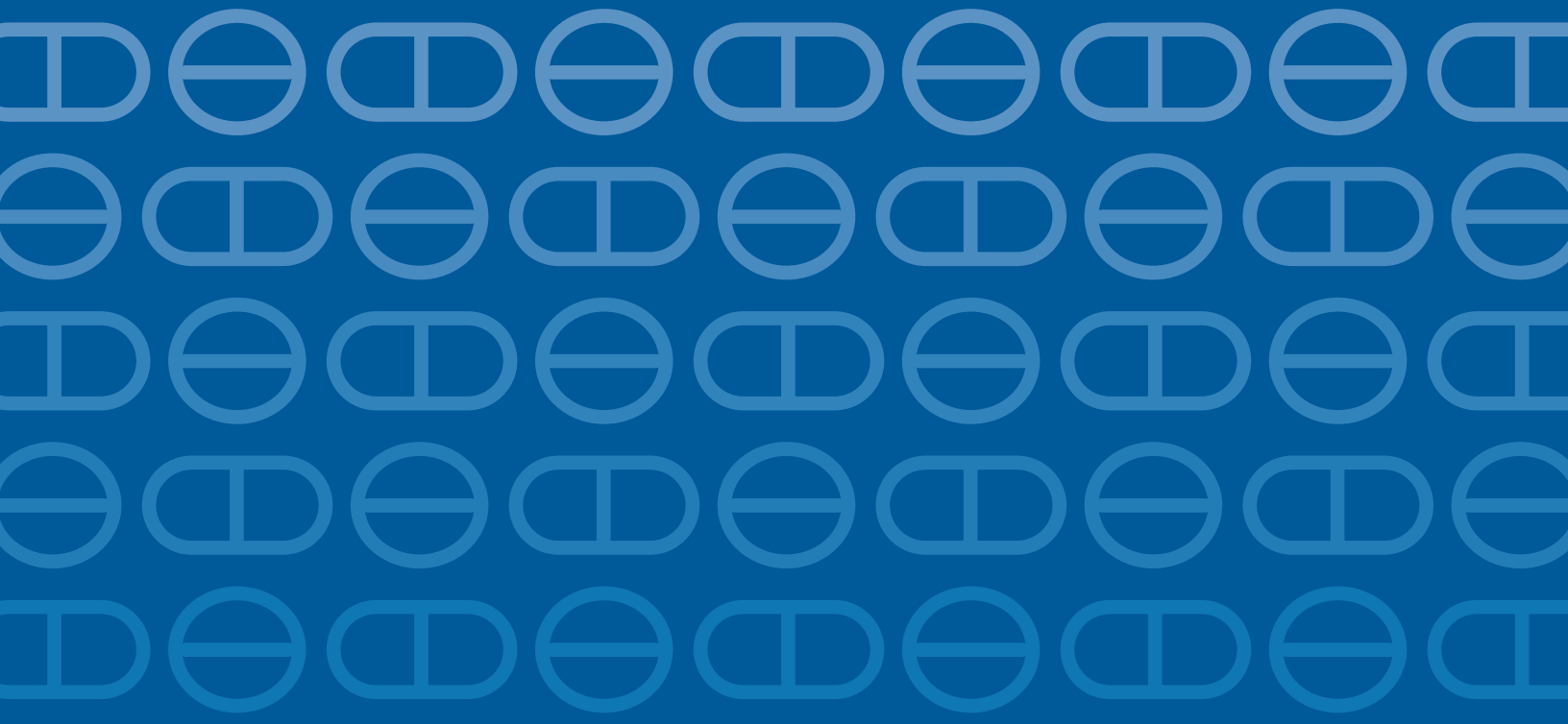
Alosa Health

Bringing unbiased evidence to clinical care

Biosimilars in clinical practice

A non-inflammatory approach to the most recent evidence and regulations



Biosimilars in clinical practice

The most recent evidence and regulations

Principal Authors: Christopher L. Cai, M.D., Jacob S. Riegler, M.D., M.B.A., M.S.B.E., and Benjamin N. Rome, M.D., M.P.H.

Series Editors: Jerry Avorn, M.D., Aaron S. Kesselheim, M.D., J.D., M.P.H. (principal editors), Sally McNagny, M.D., M.P.H., Dawn Whitney, M.S.N./Ed., R.N., Paul Fanikos, RPh, MPA/HA, Ellen Dancel, PharmD., M.P.H.

Medical Writer: Stephen Braun

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

Biosimilars in clinical practice

Activity Overview:

The goal of the educational program is to expand clinicians' understanding of the development, evaluation, and regulatory requirements for biologics and biosimilars, and to summarize the evidence concerning therapeutic efficacy, safety, and immunogenicity of biosimilars compared to reference biologics.

Learning Objectives:

After completing this activity, participants will be able to:

- Describe the regulatory pathways and criteria used by the U.S. Food and Drug Administration (FDA) for approval of biosimilar medications.
- Summarize the clinical trial evidence comparing biosimilar efficacy, safety, and immunogenicity data compared to reference biologics.
- Recognize the safety and clinical outcomes related to switching from originator to biosimilar, regardless of interchangeability designation.
- Explain the potential economic impact of biosimilars on health care resource use.

Target Audience:

The educational program is designed for clinicians who are likely to prescribe biologic and/or biosimilar medications to their patients.

Disclosures:

This material is provided by Alosa Health, a nonprofit organization which accepts no funding from any pharmaceutical company. All individuals including planners, authors, reviewers, academic detailers, staff, etc., who are in a position to control the content of this educational activity have reported no financial relationships related to the content of this activity.

Faculty and Planners:

Christopher L. Cai, M.D., is a Research Fellow in Medicine at Harvard Medical School. Dr. Cai has no relevant financial relationships to disclose.

Jacob Riegler, M.D., M.B.A., M.S.B.E., is a medical resident at Cambridge Health Alliance and researcher at the Harvard Business School. Dr. Riegler has no relevant financial relationships to disclose.

Benjamin N. Rome, M.D., M.P.H., is an Assistant Professor of Medicine at Harvard Medical School, a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, and a primary care physician. His research focuses on the affordability of prescription medications, including generic and biosimilar competition. Dr. Rome has no relevant financial relationships to disclose.

Jerry Avorn, M.D., is a Professor of Medicine at Harvard Medical School and emeritus Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 45 years. Dr. Avorn has no relevant financial relationships to disclose.

Aaron S. Kesselheim, M.D., J.D., M.P.H., is Professor of Medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital. Dr. Kesselheim has no relevant financial relationships to disclose.

Sally McNagny, M.D., M.P.H., is the Chief Medical Officer at Alosa Health. Dr. McNagny has no relevant financial relationships to disclose.

Dawn Whitney, M.S.N./Ed., R.N. is a Clinical Educator at Alosa Health. She is a lecturer in the School of Nursing and Health Sciences at the University of Massachusetts - Boston and Bouvé College of Health Sciences at Northeastern University. Ms. Whitney has no relevant financial relationships to disclose.

Paul Fanikos, RPh, MPA/HA, is the Chief Operating Officer at Alosa Health. Mr. Fanikos has no relevant financial relationships to disclose.

Ellen Dancel, PharmD, M.P.H., is the Director of Clinical Materials Development at Alosa Health. Dr. Dancel has no relevant financial relationships to disclose.

Stephen Braun, B.A. is a medical writer based in Amherst, MA. Mr. Braun has no relevant financial relationships to disclose.

Candice Gillett, PPH is the Program Manager, Joint Provider Services with Knowfully Medical Education. Ms. Gillett has no relevant financial relationships to disclose.

Reviewers:

Daniel H. Solomon, MD, MPH, is a Professor of Medicine at Harvard Medical School and Chief of the Section of Clinical Sciences in Rheumatology and is co-appointed in the Division of Pharmacoepidemiology and Pharmacoeconomics. The focus of his research is health services research, quality of care, and pharmacoepidemiology as it pertains to rheumatic diseases and osteoporosis. Dr. Solomon is Chair of the Quality of Care Committee of the American College of Rheumatology. Dr. Solomon has no relevant financial relationships to disclose.

Scott J. Hershman, M.D., FACEHP, CHCP, is Senior Director of Accreditation, Compliance, and Joint Providership for Knowfully Medical Education. Dr. Hershman has no relevant financial relationships to disclose.

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Introduction

For decades, most new medications have been small molecules that contain fewer than 100 atoms and can be chemically synthesized. Small molecule drugs are relatively easy to replicate and can be manufactured at different sites with a high degree of precision and consistency. As a result, when patent protection expires for a small molecule medication, one or more other manufacturers can introduce chemically identical generic versions.

By contrast, biologic medications are large and complex—composed of thousands, or tens of thousands of atoms—and are most often derived from living biological processes. During the late 20th century, the development of therapeutic biologics surged with the advent of genetic engineering and cell culture techniques allowing for the reliable, safe production of human hormones, vaccines, blood products, gene and cell therapies, and other bioengineered drugs.

Some examples of biologic medications are:

- protein products
  - monoclonal antibodies used to treat immunologic conditions and cancer
  - some hormone analogues, including insulins
- cell and gene therapies
  - chimeric antigen receptor (CAR) T-cell therapies used in oncology
  - gene therapies to treat rare conditions such as hemophilia and sickle cell disease
- products derived from human blood or plasma
  - albumin, immunoglobulin replacement, clotting factors
- vaccines

The number of new biologics approved by the U.S. Food and Drug Administration (FDA) has increased markedly in recent years. In 2024, a third of new drugs approved by the FDA were biologics, with about a dozen new biologics being approved each year.[1]

Figure 1: Novel drugs approved by the FDA in 2024[1]

Biologics accounted for 1 in 3 new medications in 2024.[2]

Modern biologics can be extremely expensive—ranging from tens of thousands of dollars per year of treatment to millions of dollars for a single dose.[2] Biologics make up only 5% of U.S. prescriptions but accounted for 51% of total drug spending in 2024.[3] These high costs pose a burden on the health care system in general, and potentially on individual patients.

One response to the high costs of biologics has been the development of biosimilar medications: biologic products with no clinically meaningful differences from an existing FDA-approved reference biologic that are made by a different manufacturer. As will be detailed in this evidence document, biosimilars are as safe and effective as reference biologics, but they have yet to be as widely adopted and accepted as they could be.

This evidence document summarizes the evidence supporting the safety and effectiveness of biosimilars and reviews the regulatory environment in which they are evaluated and approved by the FDA. This information is designed for clinicians who prescribe biologic medications so they can better appreciate why biosimilars are an important tool to improve the affordability of medications they prescribe and be better prepared to discuss biosimilars with their patients.

BOTTOM LINE: Biologics are complex molecules often made from living cells. Use of and spending on biologics has increased significantly in the U.S. in recent years.

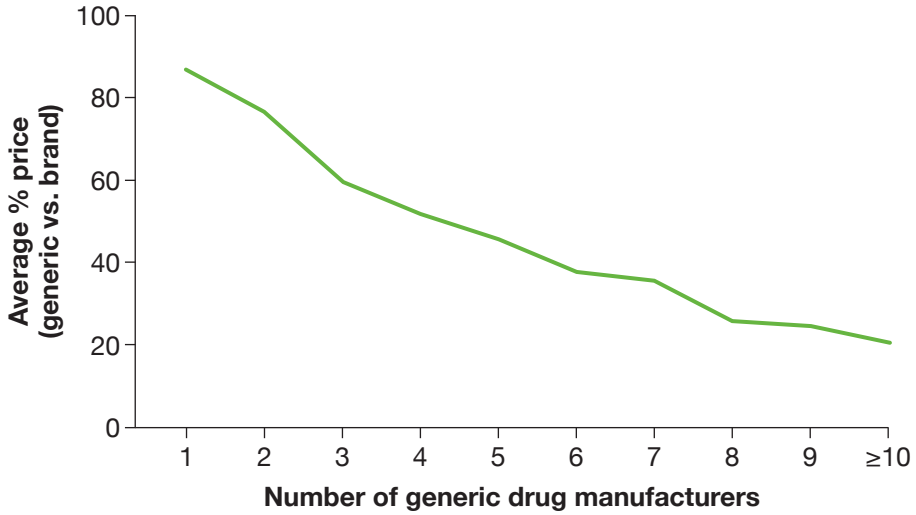
Regulation of biosimilars

Lessons from small-molecule generics

FDA approval of small-molecule generic medications is based on "bioequivalence" to the original, meaning the drugs are chemically identical and have similar bioavailability and action in the body, as demonstrated by pharmacokinetic studies in healthy volunteers. Nearly all FDA-approved generics are considered "therapeutically equivalent" to the original brand-name drug, and since the 1980s pharmacists have been allowed to substitute generic medications for name brands in all states, with required substitution in many states.[4]

Generally, clinicians are comfortable with the automatic substitution of generic for brand name small-molecule drugs. In large part due to this automatic pharmacist substitution, generics quickly replace the brand-name medication once patent protection expires. Generics account for roughly 90% of prescriptions.[5] Sufficient generic competition can lower prices by 80% or more compared to the original medication cost (Figure 2).[6]

Figure 2: The entry of additional generic manufacturers reduces generic prices compared to brand-name products[6]



Naming conventions for small molecules are straightforward, with each generic being named after the active ingredient without a brand designation (e.g., metoprolol succinate for brand name Toprol XL).

Legislation permitting biosimilars

In response to high and rising costs of biologics, the U.S. Congress enacted in 2009 the Biologics Price Competition and Innovation Act (BPCIA), which established an FDA approval pathway for biosimilars. The goal was to emulate the success of the 1984 Hatch-Waxman Act, which created a pathway for generic versions of small-molecule drugs to be developed, regulated, and sold after the expiration of patent protections for the original medication.

Because biologic medications are more complex and difficult to manufacture, the biosimilar pathway set up under the BCPIA differed in several important ways from the pathway for small-molecule generic drugs. In addition to the pharmacokinetic and pharmacodynamic studies required for generics, biosimilar manufacturers must also prove that the biosimilar and the reference biologic, or originator, are *highly similar* in terms of the structure of the molecules themselves with *no clinically meaningful differences* in terms of their clinical efficacy, safety, or immunogenicity. The FDA has typically required head-to-head clinical trials to evaluate such clinical outcomes.

While BCPIA provided an expedited pathway for biosimilars to be FDA-approved, it established a process for biosimilar interchangeability slightly different from that used for generic drugs. This process required manufacturers to conduct switching studies from the originator to the biosimilar to determine equivalent safety and efficacy, without developing an unacceptable immunologic response. Initially, only biosimilars that conducted these trials received the interchangeability designation.

Unlike small-molecule generics, biosimilars have generally had slower uptake once they reach the U.S. market. State-specific regulations concerning the substitution of biologics are more restrictive than for small-molecule drugs, with some states requiring steps such as enhanced patient consent or physician notification.[4] Only a few states have similar substitution regulations for small-molecule generics and biosimilars, which reflects the fact that many of these laws were passed prior to studies demonstrating that biosimilars are interchangeable, effective, and safe.

Naming conventions for biosimilars also differ from those for small-molecule drugs. FDA-approved biologic medications—including biosimilars—are now given a core name (i.e., risankizumab) and a random four-letter suffix at the end of the core name (e.g., risankizumab-rzaa). The suffix is a way to identify a specific biologic product made by a certain manufacturer, but the 4 letters have no specific meaning. All originator and biosimilar biologics get this four-letter suffix, but biologics approved before 2017 do not have the suffix in their name (e.g., Humira is adalimumab with no suffix). In addition to a core name with four-letter suffix, many biosimilars also have their own proprietary (or brand) names, which contrasts with small molecule generics, which typically do not have proprietary names.

Comparison of small molecule to biosimilar medications

Summarizing the key differences between these processes highlights the additional testing and hurdles for biosimilar market entry.

Table 1: Comparison of U.S. regulations of generic vs. biosimilar medications

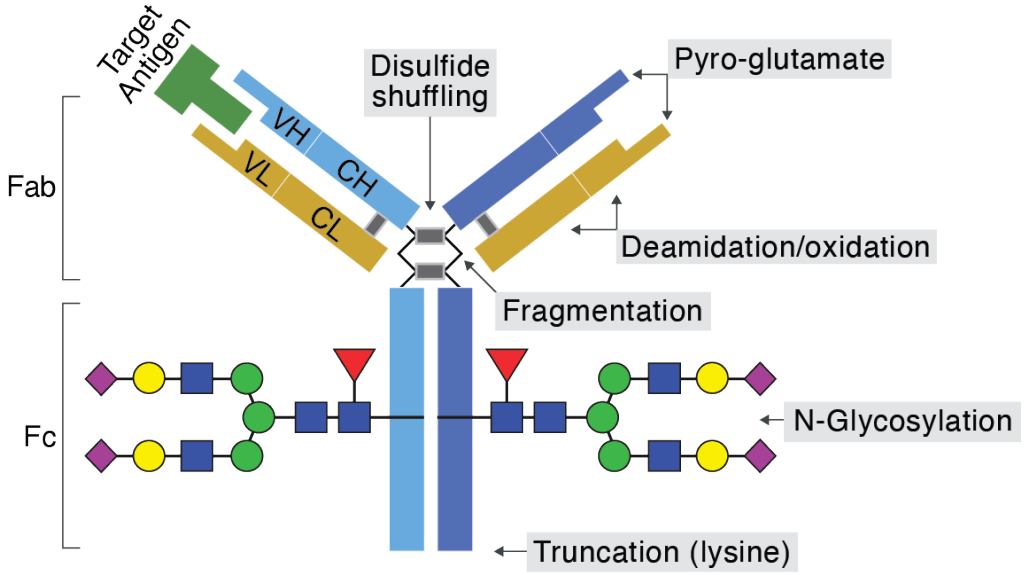
Characteristic	Generics	Biosimilars
Year FDA pathway was established	1984	2010
Standard for approval	bioequivalence	"highly similar" and "no clinically meaningful differences"
Clinical testing	pharmacokinetic studies generally in healthy volunteers	• pharmacokinetic and pharmacodynamic studies • clinical trials to establish comparative safety and efficacy
Substitutability with the original drug	• nearly all bioequivalent generics are deemed therapeutically equivalent • automatic pharmacist substitution commonplace	• separate FDA interchangeability standards • stricter rules about pharmacist substitution
Naming conventions	• no distinction between manufactures in generic names • generics usually lack trade names	• each manufacturer's version has its own 4-letter suffix • biosimilars often have their own trade names

BOTTOM LINE: The FDA biosimilar pathway was created to allow competition for biologic drugs after patent protection expires. Biosimilar medications are highly similar versions of biologic products with no clinically meaningful differences from an existing FDA-approved reference biologic. Compared to generics, biosimilars must undergo more rigorous testing of safety and effectiveness before they can be marketed.

Inherent structural variations in biologics

Biologic medications, as well as biosimilars, have inherent structural variations due to a host of factors involved in their production including the biologic processes that occur inside cells, changes in manufacturing processes, and storage conditions. For example, monoclonal antibodies are made up of primary chains of amino acids, but the structure of the antibody can be altered by extra groups of molecules attached to the sides of the main chains, such as sugars (i.e., glycosylation), and by changes in how the amino acid chain is folded. Such factors are called post-translational modifications (Figure 3).[7]

Figure 3: Types of inherent variation in a monoclonal antibody[7]

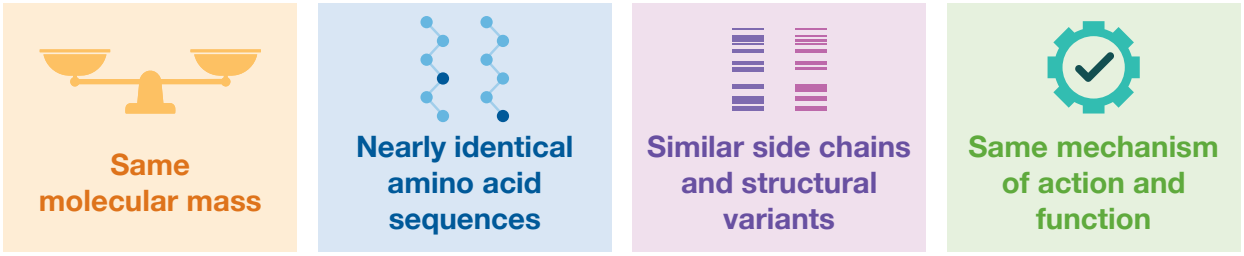


CH = constant heavy chain; CL = constant light chain; Fab = fragment antigen-binding region; Fc = fragment crystallizable region; VH = variable heavy chain; VL = variable light chain

Because of this complexity, no two batches of a biologic medication are identical. Since small variations in the molecular structure of biologics are expected and could potentially affect the efficacy or safety of the products, these variations are tightly managed by manufacturers and regulated by the FDA. Biologic manufacturers must define critical quality attributes, which are functionally important regions of the biologic molecule, as well as known molecular variants that affect function. Manufacturers also must specify testing procedures and the parameters used to test each batch of medication before shipment, the results of which must be shared in real-time with the FDA. Additional studies must be performed if any part of the manufacturing process changes in an important way or if new structural variants are identified.

Because of these complexities, biosimilar makers must conduct a battery of analytic tests to measure variation in the structure and function of their biosimilar and compare it with the reference biologic. The components of this similarity include four key areas (Figure 4).

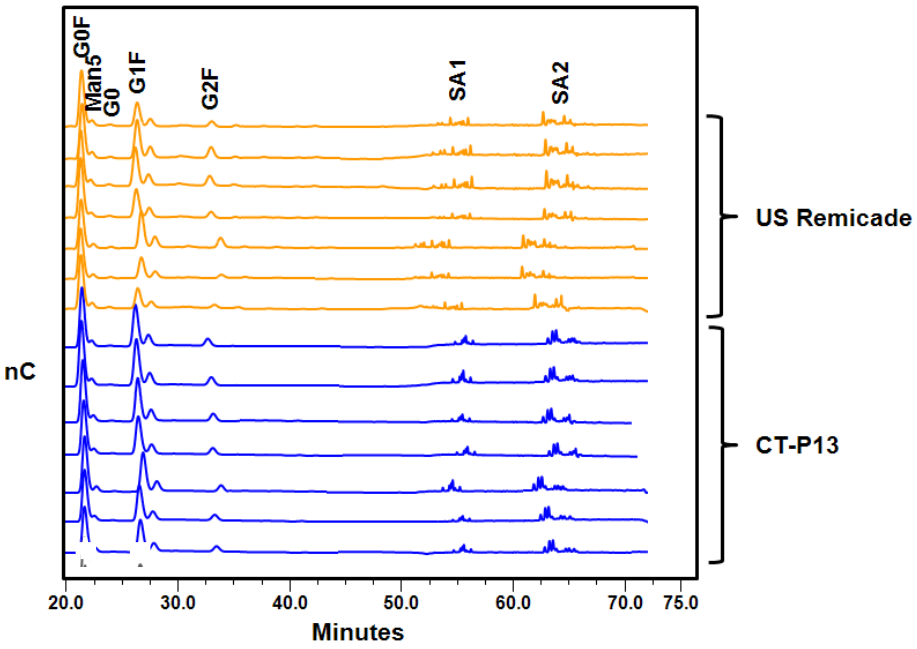
Figure 4: Biosimilars are highly similar to reference biologic molecular structure



Using the example of side chain variability, Figure 5 (next page) shows an example of glycosylation patterns between different batches of infliximab (Remicade) and a biosimilar medication (CT-P13), with

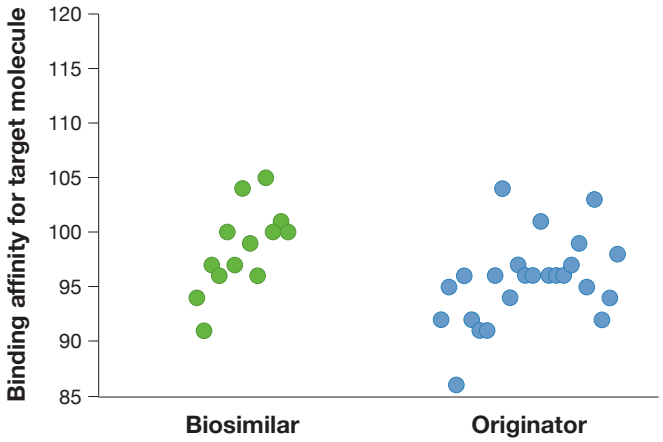
each row showing the results of an individual batch. The variation between batches of biosimilars and originators (e.g., comparing the biosimilar infliximab CT-P13 to Remicade) is similar to variations between different batches of the originator molecule (comparing Remicade to Remicade).

Figure 5: Glycosylation patterns of originator infliximab and a biosimilar[8]



Another example of variation within and between manufacturers can be seen in Figure 6, which shows variations in mechanism of action, or antibody binding affinity to the target protein VEGF-A, between batches of originator bevacizumab (Avastin) and a biosimilar, with each dot representing a different batch. These findings show the biosimilar and originator had similar mechanistic variability batch-to-batch.

Figure 6: Variation in antibody binding affinity in originator bevacizumab and a biosimilar[9]



Manufacturing consistency

In recent years, concerns have been raised about the quality of manufacturing sites for generic drugs, many of which are made in India and China. Similar concerns do not apply to biosimilars, which are typically made in similar manufacturing sites that make other originator biologics, as illustrated in Table 2.

Table 2: Manufacturing information for reference product adalimumab and biosimilars

Brand Name	Molecular name	Manufacturer	Manufacturing Sites *
Humira (originator)	adalimumab	AbbVie	U.S., Puerto Rico, Singapore, Germany
Abrilada	adalimuab-afzb	Pfizer	U.S.
Amjevita	adalimumab-atto	Amgen	U.S., Puerto Rico, Ireland, Netherlands
Cyltezo	adalimumab-adbm	Boehringer Ingelheim	U.S., Germany, Austria
Hadlima	adalimumab-bwwd	Samsung Bioepis	U.S., Netherlands, Republic of Korea
Hulio	adalimumab-fkjp	Fujifilm Kyowa Kirin Biologics	Japan
Hyrimoz	adalimumab-adaz	Sandoz	U.S., Austria, Germany, Switzerland
Idacio	adalimumab-aacf	Fresenius Kabi	U.S., Germany
Yuflyma	adalimumab-aaty	Celltrion	South Korea

*Many of these manufacturing sites are used to manufacture other originator biologic drugs (e.g., Amgen also manufactures Enbrel and Prolia at the same U.S. sites and Puerto Rico).

BOTTOM LINE: All biologics have inherent structural variation between batches, but the variation between biosimilars and the reference biologic is similar to variations between batches of the reference biologic, and structural variation is tightly controlled. Biosimilars are often manufactured in the same facilities as other reference biologics.

Biosimilar efficacy and safety

Nearly all biosimilars are compared with their reference biologics in head-to-head clinical trials. Of 23 biosimilars approved by the FDA as of October 2019, 91% were evaluated in one or more phase 3 trials comparing the efficacy of the biosimilar to the reference biologic, with a median of 538 patients per trial and median trial duration of 55 weeks.[10]

The clinical trials used to compare biosimilars to reference biologics evaluate:

- efficacy (e.g., symptomatic improvement, disease remission)
- safety (e.g., injection site reactions, infusion reactions, infections)
- immunogenicity (e.g., incidence of patients developing anti-drug antibodies)

Efficacy

A complete survey of studies comparing the efficacy of reference biologics to their biosimilars is beyond the scope of this report, but the following representative examples demonstrate the strength of the evidence supporting therapeutic efficacy across some selected disease conditions.

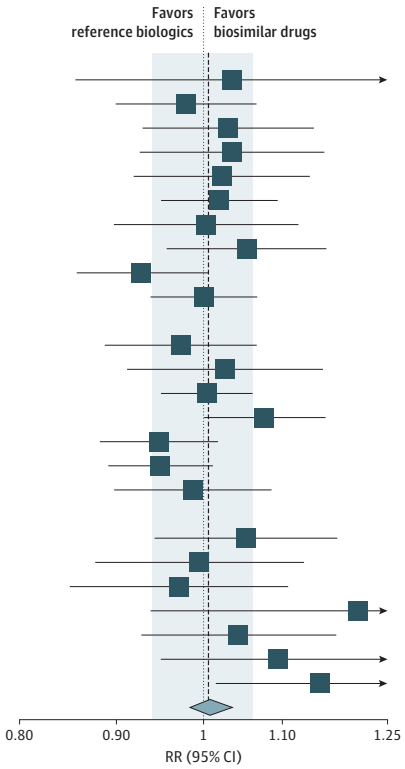
Rheumatoid arthritis

A 2023 meta-analysis of 25 studies (N=10,642) comparing three tumor necrosis factor (TNF)-alpha inhibitors (adalimumab, etanercept, infliximab) and their associated biosimilars found no significant differences in symptom improvement assessed on the widely used American College of Rheumatology symptom score (ACR20) between the reference biologics and the biosimilars (overall relative risk 1.01; 95% CI: 0.98-1.04) (Figure 7).

Figure 7: Meta-analysis of head-to-head trials comparing reference biologics to biosimilars[11]

A ACR20

Study	Biosimilars Events/total patients, No.	Reference biologics Events/total patients, No.	RR (95% CI)
Adalimumab			
Jani et al,[47] 2015	41/50	42/53	1.03 (0.86-1.25)
Alten et al,[48-54] 2017	269/363	271/358	0.98 (0.90-1.07)
Cohen et al,[55,56] 2017	194/260	189/261	1.03 (0.93-1.14)
Jamshidi et al,[57] 2017	59/64	57/64	1.04 (0.93-1.16)
Cohen et al,[61,62] 2018	216/308	201/293	1.02 (0.92-1.14)
Fleischmann et al,[58-60] 2018	248/289	234/278	1.02 (0.95-1.09)
Weinblatt et al,[63,64] 2018	173/239	171/237	1.00 (0.90-1.12)
Edwards et al,[65] 2019	123/139	111/133	1.06 (0.96-1.17)
Wiland et al,[66,67] 2019	111/127	130/138	0.93 (0.86-1.00)
Kay et al,[69,70] 2021	248/285	240/276	1.00 (0.94-1.07)
Etanercept			
Emery et al,[71-73] 2015	193/247	188/234	0.97 (0.89-1.07)
Bae et al,[74] 2016	96/115	96/118	1.03 (0.91-1.16)
Odell et al,[75,76] 2016	233/256	232/256	1.00 (0.95-1.06)
Matsuno et al,[77,78] 2017	153/164	143/165	1.08 (1.00-1.16)
Matucci-Cerinic et al,[79,80] 2018	147/167	144/155	0.95 (0.88-1.02)
Yamanaka et al,[81] 2020	226/263	230/254	0.95 (0.89-1.01)
Strusberg et al,[82] 2021	85/92	44/47	0.99 (0.90-1.09)
Infliximab			
Yoo et al,[83-85] 2013	182/248	175/251	1.05 (0.94-1.00)
Kay et al,[86,87] 2014	108/127	53/62	0.99 (0.88-1.13)
Choe et al,[88-90] 2015	148/231	163/247	0.97 (0.85-1.11)
Takeuchi et al,[91] 2015	39/50	33/51	1.21 (0.94-1.55)
Matsuno et al,[92] 2018	104/123	90/111	1.04 (0.93-1.17)
Lila et al,[93] 2019	200/280	90/138	1.10 (0.95-1.26)
Genovese et al,[94] 2020	190/279	165/279	1.15 (1.01-1.31)
Bayesian random-effects summary RR (95% CrI) Posterior probability of equivalence = 100%			**1.01 (0.98-1.04)**



Psoriasis

In a meta-analysis of 14 trials (N=5,991) and three cohort studies (N=1,130) comparing biosimilar versions of TNF-alpha inhibitors vs. reference biologics to treat psoriasis, using the standard Psoriasis Area and Severity Index (PASI) scale for quantifying the percentage of affected body surface area, 80-90% of patients had ≥75% improvement in PASI scores regardless of whether they were treated with the reference biologic or a biosimilar (Table 3).[12]

Table 3: Meta-analysis of studies comparing efficacy of reference TNF-alpha inhibitor vs. biosimilar in PASI-75 scores[12]

	Biosimilar		Originator biologic		Treatment difference, MD (95% CI), %
	N	Mean (SD), %	N	Mean (SD), %	
Week 16 (Range 12-20)					
Adalimumab					
Amjevita	172	80.9 (24.2)	173	83.1 (25.2)	-2.2 (-7.4 to 3.0)
AVT02	205	89.2 (1.6)	207	86.9 (1.7)	2.3 (-1.3 to 5.9)
BCD-057	168	77.5 (20.9)	164	80.4 (16.9)	-2.9 (-7.0 to 1.2)
Cyltezo	149	83.7	149	82.1	1.7 (-2.7 to 6.0)
Hyrimoz	191	60.7 (1.5)	192	61.5 (1.6)	0.8 (-3.2 to 4.8)
HLX03	131	83.5	130	82	1.5 (-3.9 to 6.8)
M923	261	86.2 (20.1)	263	86.8 (15.8)	-0.6 (-3.7 to 2.5)
Idacio	203	90.6 (11.3)	191	91.7 (9.9)	-1.1 (-3.2 to 1.0)
Etanercept					
Erelzi	239	56.1 (1.1)	241	55.5 (1.1)	-0.6 (-3.5 to 2.2)
CHS-0214	228	76.7 (21.1)	226	73.4 (25.0)	3.3 (-1.0 to 7.6)
Ustekinumab					
Steqeyma	256	86.1 (14.8)	248	84.0 (17.5)	2.1 (-0.7 to 4.9)
Week 52 (range 48-56)					
Adalimumab					
Amjevita	134	87.2 (19.6)	70	88.1 (21.0)	-0.9 (-5.1 to 3.3)
ATV02	181	91.6 (17.8)	87	90.8 (16.6)	0.8 (-3.6 to 5.2)
BCD-057	171	86.3 (28.1)	87	90.8 (17.3)	-4.5 (-10.1 to 1.1)
HLX03	131	87.9	130	84.9	3.1 (-2.6 to 8.8)
M923	246	86.4 (22.6)	124	85.6 (21.0)	0.8 (-3.9 to 5.5)
Idacio	186	92.8 (13.6)	85	93.9 (9.6)	-1.1 (-3.9 to 1.7)
Etanercept					
CHS-0214	225	80.9 (25.1)	213	82.9 (18.6)	-2.0 (-6.1 to 2.1)

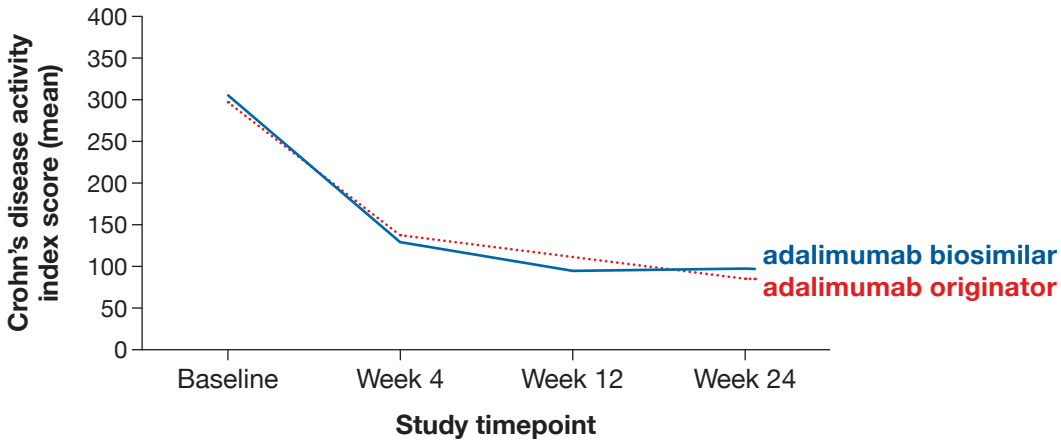
Note: proprietary names used for FDA-approved biosimilars, all others are the names used in phase 3 trials. MD: mean difference

Inflammatory bowel disease

A phase 3 randomized, double-blind study in 248 patients with Inflammatory Bowel Disease compared the reference biologic adalimumab (Humira) to a biosimilar using a marker of disease worsening (based on the Harvey-Bradshaw Index for Crohn's disease and the partial Mayo score for ulcerative colitis).[13] No significant differences in disease severity were observed at 52 weeks of follow-up.

Another phase 3 randomized, double-blind study in 147 patients with Crohn's disease compared the reference biologic adalimumab to a biosimilar using the Crohn's Disease Activity Index (CDAI) scale to assess disease activity (a combination of symptoms and laboratory data).[14] Patients in both arms improved, and no differences in activity scores were observed after 24 weeks of treatment (Figure 8).

Figure 8: Comparison of reference biologic to biosimilar for Crohn's Disease Activity Index scores[14]



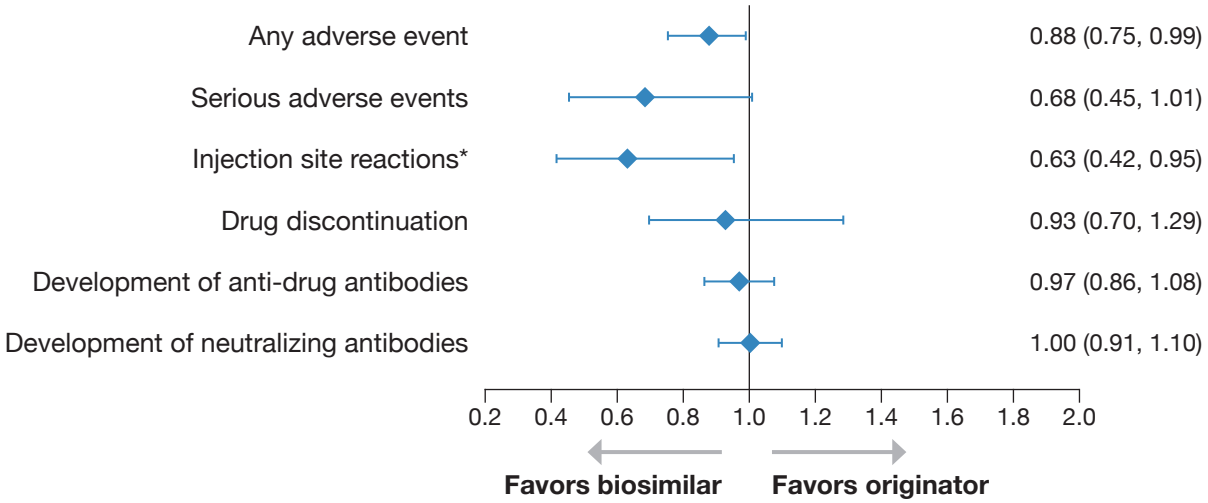
Safety

Adverse events and immunologic responses were comparable between biosimilars and originator biologic products in a range of studies.

Rheumatoid arthritis

A meta-analysis of 25 randomized trials (N=10,642) comparing a range of safety outcomes in head-to-head comparisons of a reference biologic with a biosimilar in patients with rheumatoid arthritis found similar, or lower, rates of adverse events with the biosimilars (Figure 9).[11]

Figure 9: Relative risks of adverse events in studies comparing reference biologic adalimumab with a biosimilar[11]



*This lower risk may be due to comparison of adalimumab biosimilar versions that were citrate-free to the originator version containing citrate.

Psoriasis

A meta-analysis of safety outcomes in studies comparing a reference biologic vs. several biosimilars in patients with psoriasis found no significant differences in adverse events (Table 4, next page).

Table 4: Risk ratios for safety outcomes in studies comparing a reference biologic vs. a biosimilar in patients with psoriasis at week 16[12]

	Biosimilar		Originator biologic		Risk ratio Mantel-Haenszel, random (95% CI)
	Events	Total	Events	Total	
Adalimumab					
Amjevita	117	174	110	173	1.06 (0.91-1.23)
AVT02	92	205	91	207	1.02 (0.82-1.27)
BCD-057	54	174	54	172	0.99 (0.72-1.35)
Cyltezo	66	159	71	158	0.92 (0.72-1.19)
Yusimry	133	274	122	271	1.08 (0.90-1.29)
Hyrimoz	116	231	123	234	0.96 (0.80-1.14)
M923	**169**	**285**	**194**	**285**	**0.87 (0.77-0.99)***
Idacio	114	221	117	220	0.97 (0.81-1.16)
Etanercept					
CHS-0214	191	261	199	260	0.96 (0.87-1.06)
Ustekinumab					
Steqeyma	95	256	75	253	1.25 (0.98-1.60)

Note: proprietary names used for FDA-approved biosimilars, all others are the names used in phase 3 trials. *p<0.05 = favors biosimilar

Crohn's disease

Comparable rates of adverse events were found in two studies in patients with Crohn's disease comparing a reference biologic to a biosimilar.

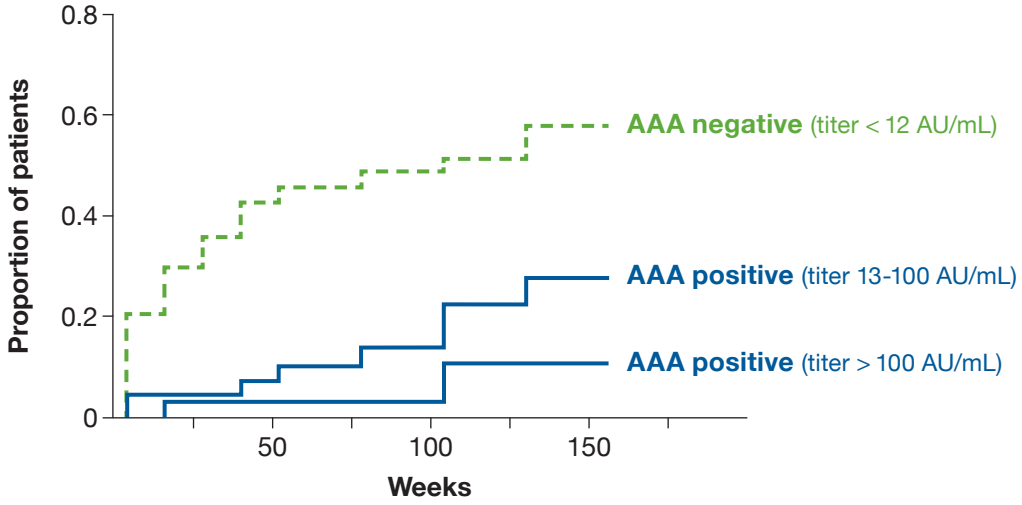
Immunogenicity

Because biologics are large foreign molecules, in some cases patients develop an immune response and make antibodies that bind to the biologic medication:

- Anti-drug antibodies (ADAs) bind to a drug and may or may not alter its function. Measures of ADA may predict a lack of response to a biosimilar.
- Neutralizing antibodies directly interfere with the binding site of a drug and its target, which makes this type of immunogenicity more likely to predict a lack of response than ADAs.

Patients who develop anti-drug antibodies are more likely to have treatment failure, as illustrated in Figure 10, which presents the results of a prospective cohort study of 272 patients with rheumatoid arthritis in which higher levels of anti-drug antibodies were associated with lower rates of disease remission. Overall, 28% of patients developed some anti-drug antibodies during three years of follow-up, and higher antibody titers were associated with worse outcomes.[15] Additionally, certain anti-drug antibodies can persist for months to years after drug withdrawal, which limits future therapeutic choices.[16]

Figure 10: Rates of sustained minimal disease activity in patients with rheumatoid arthritis and three levels of anti-adalimumab antibodies (AAA)[15]



The previously-cited meta-analysis of 25 randomized trials (N=10,642) in patients with rheumatoid arthritis also compared rates of anti-drug antibodies and neutralizing antibodies and found no significant differences in either when comparing adalimumab with a biosimilar (see Figure 9 above).

BOTTOM LINE: Randomized controlled trials have consistently found that biosimilars are as safe and effective as original biologic medications and have similar risks of immunogenicity.

Safety of switching to biosimilars

Because biosimilars are less costly than the original, in some cases patients who take a biologic medication may be asked to switch to a biosimilar by their insurance provider or may request to do so. When the biosimilar pathway was first created, Congress was concerned about such switching happening automatically without input from the prescriber, as is common for generic drugs. Thus, Congress specified separate standards for biosimilars to be deemed "interchangeable" with the original, meaning that they could be "substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

To be deemed interchangeable, the FDA regulations required that a biosimilar:[17]

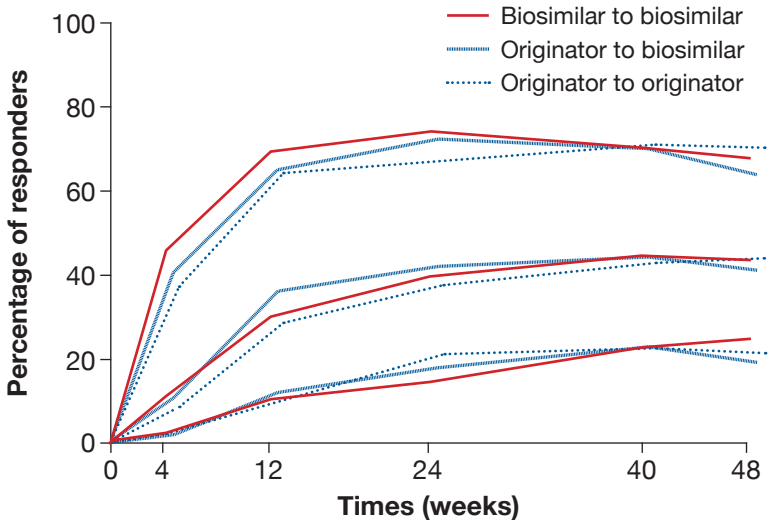
- "can be expected to produce the same clinical result as the reference product in any given patient"
- "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

To meet this interchangeability standard, the FDA required that companies perform switching studies to measure the effects of patients switching between the biosimilar and reference biologic in terms of pharmacokinetic, pharmacodynamic, immunogenicity, safety, and efficacy endpoints. Because of this requirement, many randomized controlled trials have been performed that demonstrate the safety and effectiveness of switching between biologics and biosimilars. Some examples of the evidence from these switching studies are described below.

Rheumatoid arthritis

The VOLTAIRE-RA switching study randomized 645 patients to either originator adalimumab or a biosimilar; patients in the originator group were then randomized at week 24 to either remain on the reference product or switch to the biosimilar.[18] This study found no significant differences in scores on the ACR20 response criteria for rheumatoid arthritis among patients who were switched between originator adalimumab and its biosimilar (Figure 11).

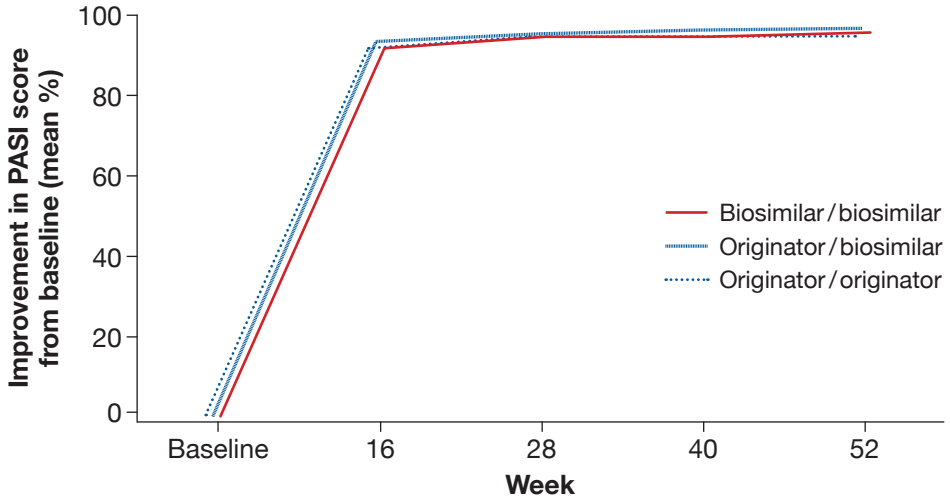
Figure 11: Percentage of responders (three ACR score levels) among those who either remained on a reference product or biosimilar, or who switched from the reference product to a biosimilar[18]



Psoriasis

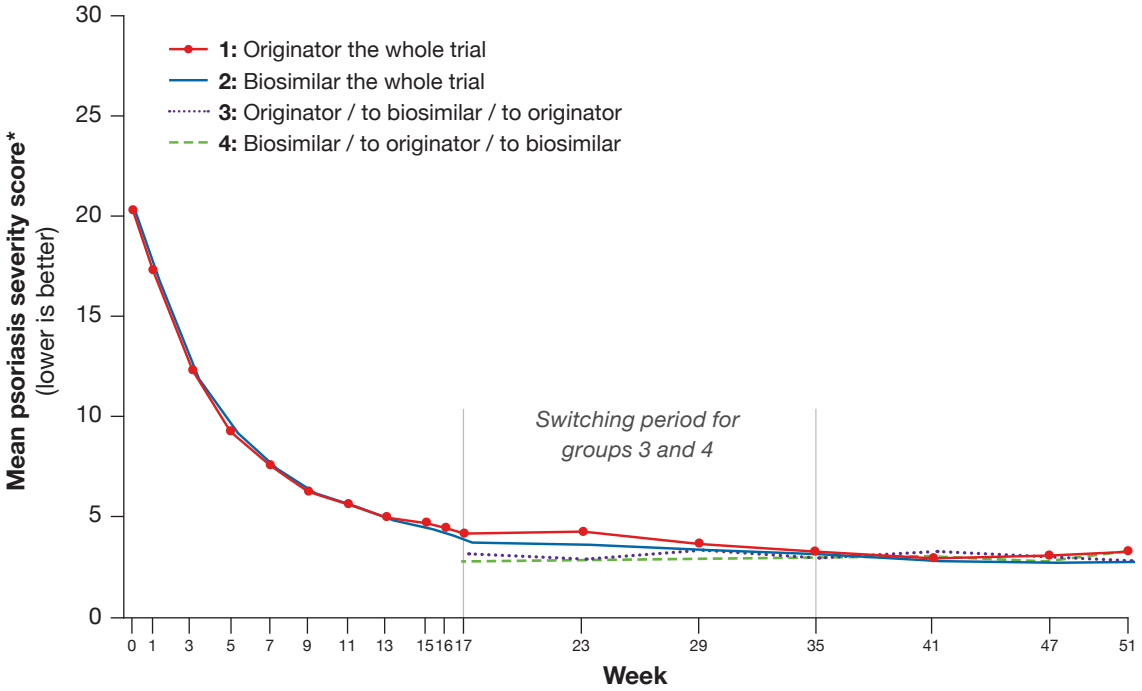
Another switching study (N=581) in patients with moderate-to-severe plaque psoriasis compared efficacy and immunogenicity in those treated with the reference biologic ustekinumab (Stelara) or a biosimilar.[19] No significant differences in efficacy were observed (Figure 12, next page), and those treated with the biosimilar actually had a lower risk of developing anti-drug antibodies.

Figure 12: Efficacy and immunogenicity results from a switching study comparing originator ustekinumab vs. a biosimilar[20]



In another double-blind trial, patients with psoriasis were randomized to receive the originator adalimumab or a biosimilar. After 17 weeks, patients were randomized again to either switch back and forth multiple times between adalimumab and a biosimilar or to remain on the same version throughout the trial (Figure 13). There was no difference in clinical responses (measured using the PASI score) between patients who switched or remained on the same version throughout the trial.[21]

Figure 13: Psoriasis severity over time with two cohorts who switched between originator adalimumab and a biosimilar vs. continuing baseline biologic[21]



*Disease severity was measured by the Psoriasis Area and Severity Index (PASI).

Inflammatory bowel disease

The effect of switching multiple times between a reference biologic and a biosimilar was evaluated in a real-world study of 297 patients with inflammatory bowel disease treated with originator infliximab or two different biosimilars.[22] No association was observed in rates of adherence to treatment, remission, or biochemical or fecal biomarkers for inflammation with different numbers of switches.

FDA Analysis of switching studies

In 2023, the FDA published a meta-analysis that included 5,252 patients from 31 switching studies for 21 biosimilar medications and found:[23]

- no differences in safety outcomes, including death, serious adverse events, or treatment discontinuation
- similar incidence of anti-drug antibody development among patients switched vs. not switched
- similar immune-related adverse events (e.g., hypersensitivity, injection site reactions)

The FDA's findings have been replicated in two additional reviews, one of 21 studies (N=2,802),[24] and another of 17 studies (N=6,562).[25] The safety of switching is also supported by an analysis from Europe analyzing more than 1 million patient years of treatment data with 29 biosimilars. No differences were observed in safety, efficacy, or immunogenicity.[26,27]

BOTTOM LINE: Switching between biologics and biosimilars has been thoroughly studied. The evidence demonstrates that patients can switch back and forth between originator biologics and biosimilars, without any impact on effectiveness, safety, or immunogenicity.

Confidence across indications

Many biologic medications have multiple indications because their mechanisms of action can be useful in treating disease states (e.g., auto-immune diseases) that may vary in presentation but arise from similar biological causes. Biosimilars are generally studied in a single clinical trial of patients with one of the original biologic's indications. Biosimilar manufacturers are permitted to extrapolate these findings to justify approval for other populations that were not directly studied in the clinical trial.

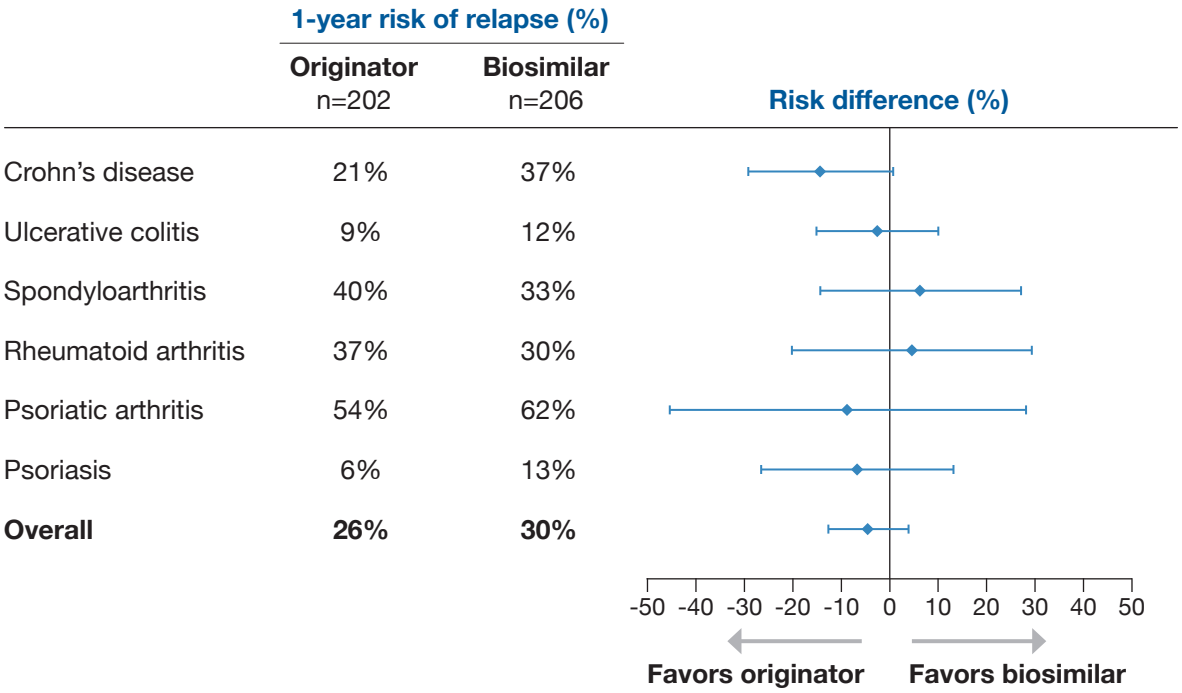
Such extrapolation must be scientifically justified by the biosimilar manufacturer based on information about:

- the reference product for each approved indication, including its mechanism of action
- whether any differences exist between the biosimilar and the reference product that might affect its use in other non-studied populations

The clinical relevance of such extrapolation was demonstrated in a switching trial of an infliximab biosimilar that included patients with many different indications.[13] The NOR-SWITCH study randomized 482 adults with Crohn's disease, ulcerative colitis, spondylarthritis, rheumatoid arthritis, psoriatic arthritis, or plaque psoriasis who had been taking infliximab for at least six months to either remain on originator

infliximab or switch to a biosimilar. No differences were seen in disease severity, adverse effects or discontinuation (Figure 14).

Figure 14: Risk of disease worsening within one year in patients on infliximab or a biosimilar[13]



BOTTOM LINE: Even though biosimilars are often studied in clinical trials for one or a few conditions, their safety and effectiveness for other conditions may be extrapolated, and evidence suggests that biosimilars are safe and effective across a range of indications.

Experience with biosimilars to date

The first biosimilar was approved by the FDA in 2015 and as of June 2025 the FDA had approved 75 biosimilars for 19 reference biologics.[28] Not all of them, however, are available at present. Figure 15 lists the 15 biologics for which one or more biosimilars were available as of September 2025.

Figure 15: Originator biologic medications for which biosimilars are available

Immunology
- adalimumab (Humira)
- eculizumab (Soliris)*
- infliximab (Remicade)
- tocilizumab (Actemra)*
- ustekinumab (Stelara)*

Oncology
- bevacizumab (Avastin)
- filgrastim (Neupogen)
- pegfilgrastim (Neulasta)
- rituximab (Rituxan)
- trastuzumab (Herceptin)

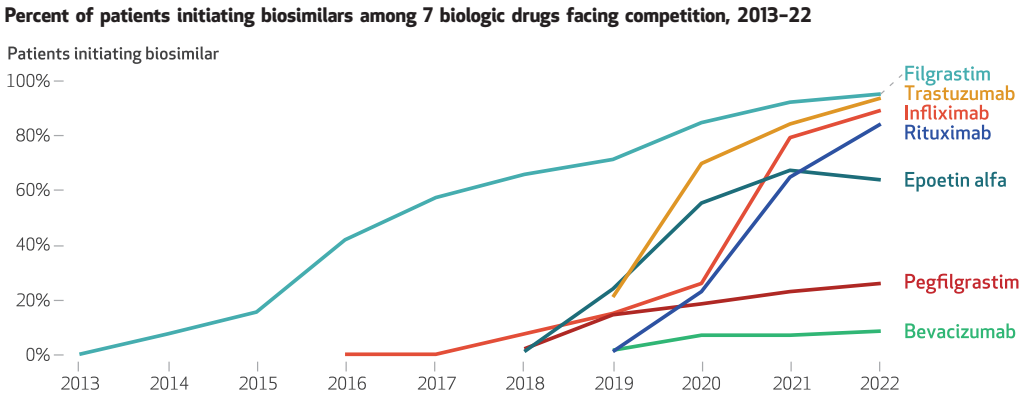
Ophthalmology
- aflibercept (Eylea)*
- ranibizumab (Lucentis)

Other
- epoetin alfa (Epogen)
- denosumab (Prolia)*
- insulin glargine (Lantus)

* Biosimilar competition began in 2024 or 2025 for these originator biologics

Only 19% of biologics without patent protection have a marketed biosimilar.[29] The introduction of biosimilar competition initially lowers prices by about 25%, with more competition decreasing prices further—by as much as 90% compared to the original biologic.[29] As illustrated in Figure 16, the uptake of biosimilars is highly variable across medications.

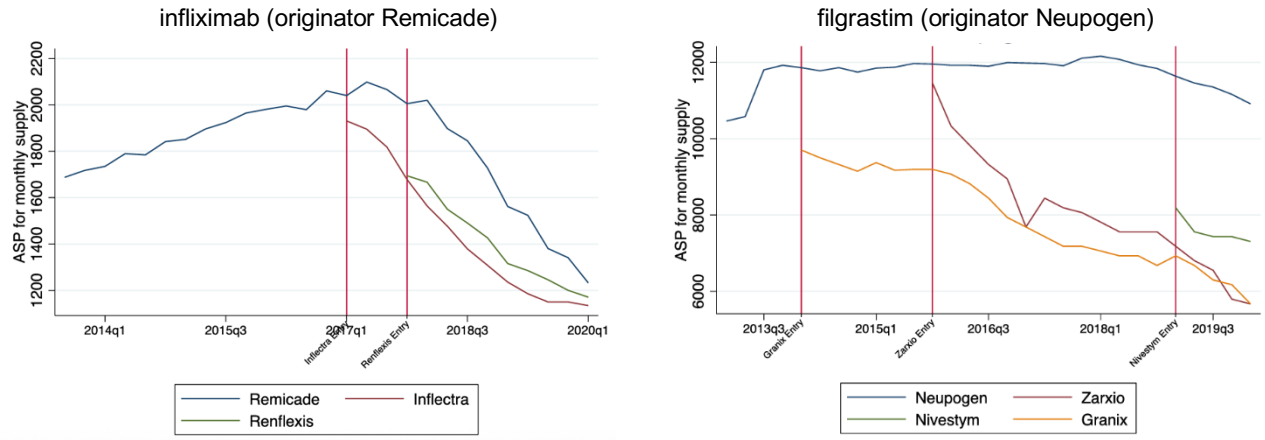
Figure 16: Uptake of biosimilar medications over time[30]



SOURCE Authors' analysis of data from Optum Clinformatics Data Mart for the period 2013–22.

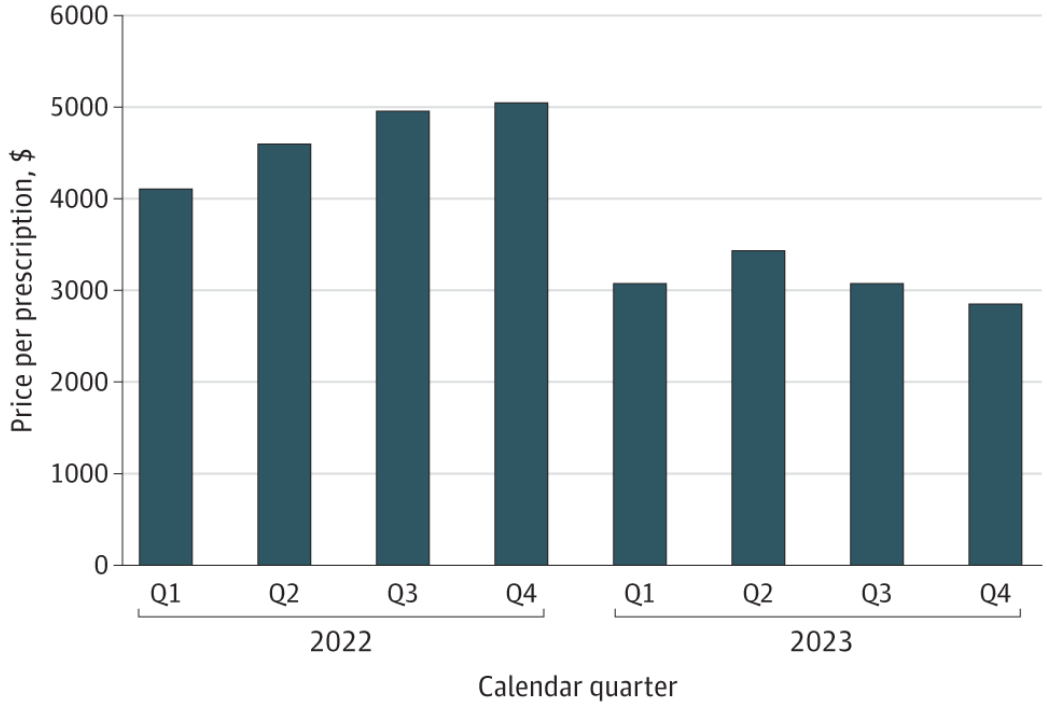
With the introduction of biosimilars prices for both the reference biologic and their biosimilars typically (but not always) decline with time (Figure 17, next page).

Figure 17: Cost trends for two biologics and their biosimilar competitors[31]



Originator adalimumab (Humira) – the best-selling medication of all time[32] – faced biosimilar competition in the U.S. starting in January 2023. Although biosimilars accounted for 2% of adalimumab prescriptions by the end of 2023, spending on adalimumab decreased by nearly half during this first year, likely because the originator manufacturer was forced to offer steeper discounts in an effort to maintain market dominance and a preferred formulary position (Figure 18).[33]

Figure 18: Net per-prescription costs of originator adalimumab before and after biosimilar competition began in 2023[33]



Biosimilars have already saved an estimated $56.2 billion in U.S. health care costs through 2024,[34] but both the number of biosimilars and their overall impact have not reached their full potential. One concern

has been that competition from biosimilars has not consistently lowered out-of-pocket costs for patients.[35] In addition, of the 118 biologic drugs expected to lose patent exclusivity in the next decade, only 12 have biosimilars in development.[34]

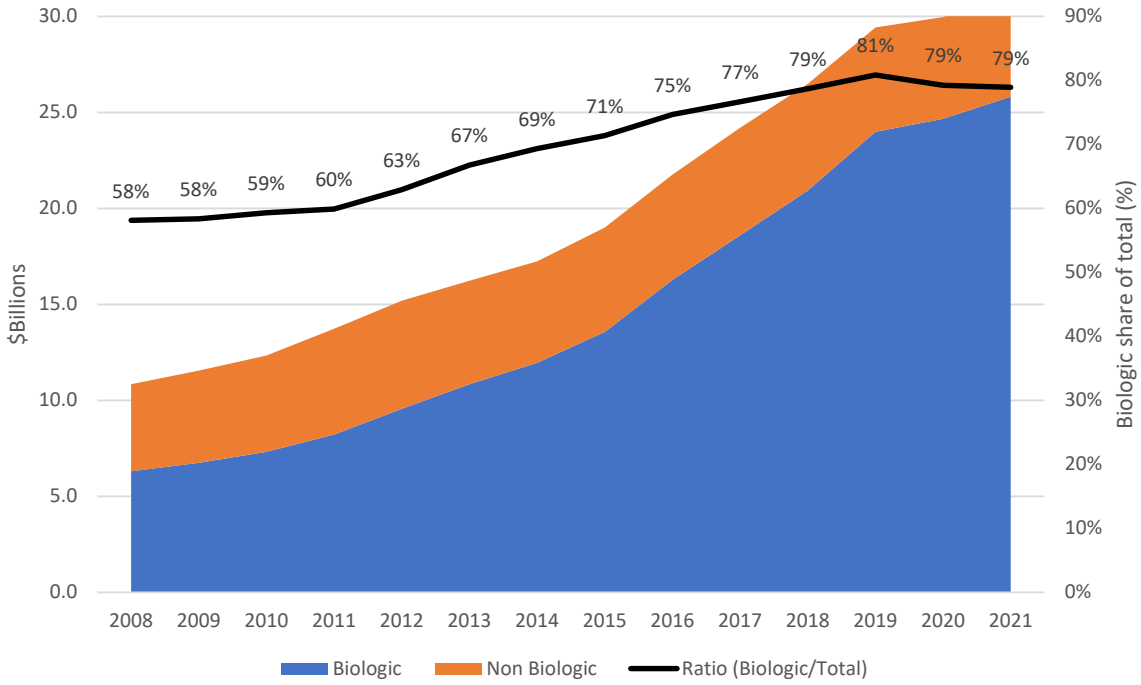
Although biosimilars are still relatively new in the U.S., there has been considerably more experience with biosimilar competition in Europe. The European Medicines Agency (EMA) established a regulatory framework for biosimilars in 2005, and the first biosimilar was approved there in 2006. To date, the EMA has approved 144 biosimilars for 25 reference biologics (nearly double the number in the U.S.). Savings to patients and health care systems in the U.S. from the use of biosimilars have been much lower than in Europe because of slower approval of biosimilars here and lower rates of switching.[36] For example, originator adalimumab faced biosimilar competition in Denmark starting in October 2018 when three biosimilars were approved. Within two months, biosimilars accounted for 95% of adalimumab use and costs decreased by 83%.[37] Similar rapid biosimilar adoption and cost declines were observed with infliximab starting in 2015.[38]

BOTTOM LINE: The FDA has approved 75 biosimilars since 2015, although uptake of these biosimilars has been variable. Despite these limitations, biosimilars tend to lower prices and offer meaningful health care savings, although this has not always translated into savings for patients using these medications. Adoption of biosimilars has been more rapid in Europe than the U.S., with correspondingly greater and more rapid cost savings.

Future trends in biosimilars

Spending on biologic medication has increased rapidly in recent years. For example, Medicare Part B spending on prescription medications administered in outpatient clinics and hospitals more than doubled from 2008 to 2021, with 89% of that growth attributable to increased spending on biologics.[39] Spending on biologics has particularly increased for non-retail clinician-administered drugs, such as intravenous infusions administered in an office or hospital setting. These clinician-administered medications are reimbursed by Medicare Part B, for which spending on biologics more than tripled from 2008 to 2021. Biologics represented nearly 80% of Medicare Part B prescription drug spending in 2021.[40]

Figure 19: Medicare Part B spending on biologics vs. non-biologic medications[39]



Source: Analysis of physician office, durable medical equipment, and outpatient claims data 2008-2021 by Acumen for ASPE.

Acceptance and use of biosimilars is slowly increasing among U.S. clinicians in the specialties most likely to prescribe biologics. A survey of 401 specialists found that 89% were comfortable prescribing biosimilars to treatment-naïve patients, and 80% were comfortable switching patients already taking a reference biologic to a biosimilar.[41] However, some hesitations about biosimilars remain. Only 40%, for example, were comfortable with their patients being switched to a biosimilar by a third party (e.g., pharmacists), and 67% wanted a "dispense as written" option to prevent substitution to a biosimilar.

To date, the passage of the BPCIA has not resulted in savings from biosimilars to the level policymakers may have hoped. The regulatory approval and availability of biosimilars has been slow, the uptake of biosimilars by prescribers has been modest, and savings for patients have been inconsistent.[42]

One issue has been a lack of automatic pharmacist substitution of biosimilars for a reference biologic. This is related to the standards embedded in the BPCIA, which are more extensive than those governing approval of generic small-molecule medications, as well as variations across state regulations.

Based on current evidence from switching studies such as those summarized above in 2024 the FDA introduced a draft of revised guidance that would allow biosimilars to be deemed interchangeable without separate switching studies.[43] As of September 2025, this guidance had not been finalized. Some FDA regulators have proposed that Congress should eliminate the separate interchangeability standard for biosimilars because it creates confusion and because existing biosimilar standards are sufficient to ensure that biosimilars can safely be interchanged with a reference biologic.[44] Such switching studies are not required in Europe.

Professional society endorsements

The growing use of biosimilars has been endorsed by three major specialty societies whose members frequently prescribe biologics:

American College of Rheumatology	*"Biosimilars are considered equivalent to FDA-approved originator DMARDs [Disease Modifying Anti-Rheumatic Drugs]."*[45]
American Gastroenterological Association	*"Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy in terms of therapy selection."*[46]
American Academy of Dermatology Association	*"TNF-α biosimilars approved by the FDA should be considered similar to the reference branded version of the drug. The aforementioned guidelines/recommendations should apply similarly to biosimilar versions of TNF-α inhibitors"*[47]

BOTTOM LINE: While the FDA continues to have separate regulatory standards for biosimilar interchangeability with a reference biologic, it may not require formal switching studies going forward. Major professional societies have endorsed the use of biosimilars.

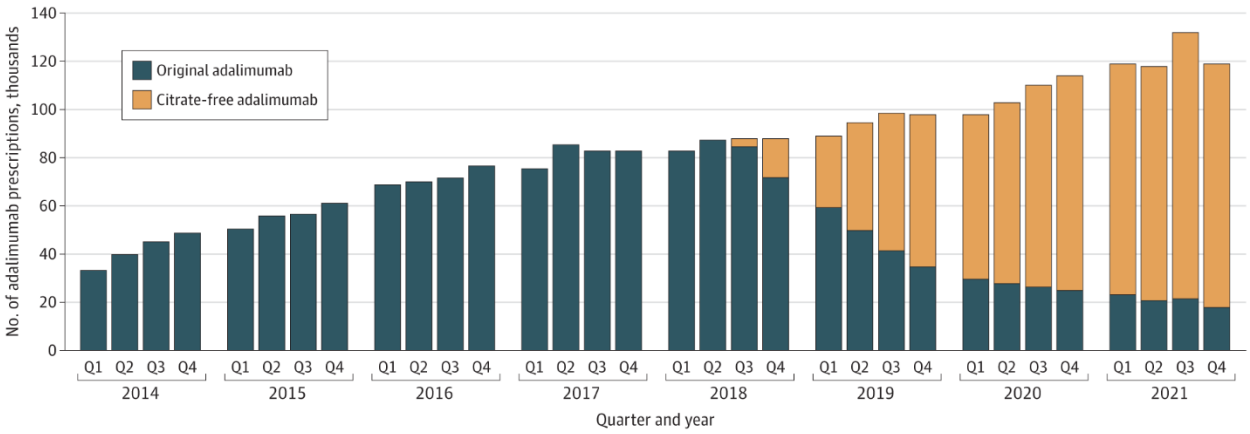
Biosimilars for adalimumab and ustekinumab

The evidence summarized in this report documents the safety and efficacy of biosimilars and the rigorous manufacturing processes and regulatory requirements used to create and approve them. Two real-world case studies of a reference biologic and its biosimilars illustrate these issues.

Adalimumab

Adalimumab (Humira), approved by the FDA in 2002, is a biologic anti-TNF alpha monoclonal antibody used to treat autoimmune and inflammatory conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, and ankylosing spondylitis. In 2018, the manufacturer of originator adalimumab introduced a new version designed to cause less injection-site pain.[48] The new version removed citrate from the buffer, was more concentrated, and used a smaller gauge needle in the pen delivery device. Many patients switched to the new version as illustrated in Figure 20.

Figure 20: Market shares of the original adalimumab and the new version introduced in 2018.[49]



A number of adalimumab biosimilars have been introduced. The exact characteristics of these different biosimilars varies, with some matching the original and some matching the newer version of Humira. All of the manufacturers of biosimilar adalimumab made citrate-free versions; two also sold a version that contained citrate (Table 5).

Table 5: Characteristics of adalimumab biosimilars[50]

Biosimilar (Brand name)	Concentration		Citrate free		Designated by FDA as interchangeable	
	High	Low	Yes	No	Yes	No
adalimuab-afzb (Abrilada)		X	X		X	
adalimumab-atto (Amjevita)	X	X	X		X	
adalimumab-adbm (Cytezlo)	X	X	X		X	
adalimumab-bwwd (Hadlima)	X	X	X	X	X	
adalimumab-fkjp (Hulio)		X	X		X	
adalimumab-adaz (Hyrimoz)	X	X	X	X	X	
adalimumab-aacf (Idacio)		X	X			X
adalimumab-ryvk (Simlandi)	X		X		X	
adalimumab-aaty (Yuflyma)	X		X		X	
adalimumab-aqvh (Yusimry)		X	X			X

Originator adalimumab's market share dropped due to a shift driven both by the lower costs of biosimilars as well as decisions by some pharmacy benefit managers to remove the original adalimumab from their

formularies.[33] The price of adalimumab biosimilars can be roughly 80% lower than that of the reference product.[51]

Ustekinumab

Ustekinumab (Stelara) is a monoclonal antibody that inhibits the interleukin proteins IL-12 and IL-23. It was approved by the FDA in 2009 to treat psoriasis and approved for inflammatory bowel disease in 2016. In addition to these indications, it is also used to treat Crohn's disease, ulcerative colitis, and hidradenitis suppurativa. Most ustekinumab biosimilars have been deemed interchangeable with the reference medication by FDA (Table 6).

Table 6: Characteristics of ustekinumab biosimilars[50]

Biosimilar (Brand name)	Manufacturer	FDA approval	Market launch	Designated by FDA as interchangeable
ustekinumab-auub (Wezlana)	Amgen	October 2023	January 2025	yes
ustekinumab-ttwe (Pyzchiva)	Samsung Bioepis / Sandoz	June 2024	February 2025	yes
ustekinumab-aekn (Selarsdi)	Alvotech / Teva	April 2024	February 2025	yes
ustekinumab-kfce (Yesintek)	Biocon	November 2024	February 2025	yes
ustekinumab-aauz (Otulfi)	Formycon / Fresenius Kabi	September 2024	March 2025	yes
ustekinumab-stba (Steqeyma)	Celltrion	December 2024	March 2025	yes
ustekinumab-srlf (Imuldosa)	Dong-A ST/ Meiji Seika / Accord	October 2024	August 2025	no
ustekinumab-hmny (Starjemza)	Hikma / Bio-Thera Solutions	May 2025	N/A*	yes

* not yet marketed in the U.S. as of September 2025

Putting it all together

Biologic medications have transformed the care and improved patient outcomes for many inflammatory diseases. Biosimilars are therapeutically equivalent versions of originator, or “reference,” biologics. Minor variations in the molecular structure of biologics and biosimilars are inherent in the processes by which they are made, and such variations between a given biosimilar and the reference biologic are similar to variations between batches of the reference biologic itself. Although the safety and efficacy of biosimilars are well-established, their adoption has been slower than traditionally occurs for small-molecule generic drugs. Use of biosimilars can lead to cost savings.

Key points to consider:

- Use of and spending on biologics has increased enormously in the U.S. in recent years, placing pressure on health care costs.
- The FDA’s biosimilar approval pathway was created to facilitate establishment of a competitive market for biologic medications after patent protection expires, in an attempt to emulate the success of generic competition for small-molecule drugs.
- Biosimilars must undergo more rigorous testing of safety and efficacy before they can be marketed in the U.S.
- Clinical trials have consistently shown that biosimilars are as safe and effective and no more immunogenic than reference biologics.
- The evidence indicates that patients can safely switch to FDA-approved biosimilars, although this may not happen automatically because of FDA interchangeability designations and state pharmacy substitution laws.
- Although biosimilars are typically studied in clinical trials for one or a few conditions, their safety and effectiveness may be extrapolated to other conditions for which the reference biologic is indicated, if scientifically justified.

Appendix 1: Biosimilars for rheumatological conditions

Efficacy, safety and immunogenicity

A 2023 meta-analysis of studies comparing three TNF-alpha inhibitors (adalimumab, etanercept, infliximab) and their associated biosimilars found no significant differences in symptom improvements for rheumatoid arthritis assessed with the American College of Rheumatology symptom score (ACR20) between the reference biologics and the biosimilars. These included 25 head-to-head trials involving 10,642 patients; the overall estimate of a difference in outcomes was 1.01, indicating essentially no difference (95% CI: 0.98-1.04).[11] In an analysis of efficacy using the Health Assessment Questionnaire-Disability Index (HAQ-DI), biosimilars demonstrated equivalence in 14 trials involving 5,579 patients (the standard mean difference in HAQ-DI score was close to zero at -0.04; 95% CI: -0.11 to 0.02).

Analysis of safety outcomes found similar or lower rates of adverse events with the biosimilars (overall relative risk for adverse events favored the biosimilar, at 0.88; 95% CI: 0.75-0.99). No significant differences were found between groups in levels of anti-drug antibodies (RR 0.97; 95% CI: 0.86-1.08) or neutralizing antibodies (RR 1; 95% CI: 0.91-1.1).

Switching studies

The VOLTAIRE-RA switching study randomized 645 patients with rheumatoid arthritis to receive either adalimumab or a biosimilar; then patients in the adalimumab group were randomized at week 24 to either remain on the reference product or switch to the biosimilar.[18] This trial found no significant differences in scores on the ACR response criteria for rheumatoid arthritis among patients who were switched between adalimumab and the biosimilar, nor on measures of immunogenicity between the two groups.

A post-marketing observational study in South Korea included 112 patients with ankylosing spondylitis and rheumatoid arthritis who were initially treated with etanercept and were then switched to a biosimilar.[52] No significant differences were seen in disease activity scores or adverse events 24 weeks after the switch.

BOTTOM LINE: Extensive evidence from meta-analyses, switching studies, and post-marketing observations have found therapeutic equivalence between originator biologics for rheumatological conditions and biosimilars.

Appendix 2: Biosimilars for psoriasis

Efficacy, safety, and immunogenicity

In a meta-analysis of 14 trials (N=5,991) and three cohort studies (N=1,130) comparing biosimilar versions of TNF-alpha inhibitors vs. reference biologics to treat psoriasis, using the standard Psoriasis Area and Severity Index (PASI) scale for quantifying the percentage of affected body surface area, 80-90% of patients had ≥75% improvement in PASI scores regardless of whether they were treated with the reference biologic or a biosimilar.[12] No significant differences in any safety outcomes were observed in this analysis.

Switching studies

A switching study (N=581) in patients with moderate-to-severe plaque psoriasis compared efficacy and immunogenicity in those treated with the reference biologic ustekinumab or a biosimilar.[19] No significant differences in efficacy were observed, and the incidence of anti-drug antibodies was lower among those treated with the biosimilar, although this was not considered clinically meaningful.

In a double-blind trial, patients with psoriasis were randomized to switch back and forth multiple times between adalimumab and a biosimilar, or were kept on adalimumab. There was no difference in clinical outcomes.[21]

BOTTOM LINE: Evidence from a meta-analysis and switching studies demonstrated therapeutic equivalence for dermatological conditions between originator biologics and biosimilars.

Appendix 3: Biosimilars for inflammatory bowel disease

Efficacy, safety and immunogenicity

The VOLTAIRE-CD phase 3 randomized, double-blind trial studied 147 patients with Crohn's disease to compare the reference biologic adalimumab to a biosimilar using the CDAI scale to assess disease activity (a combination of symptoms and lab reports).[14] At week 4, 90% of patients in the biosimilar group and 94% in the adalimumab reference group had a clinical response, not a significant difference (adjusted RR 0.945; 90% CI: 0.87–1.03). In a safety analysis 63% of patients in the biosimilar group and 56% in the adalimumab group had an adverse event during weeks 0–24, and 43% vs. 45% had adverse events during weeks 24–56. These differences were also not statistically significant.

Switching studies

The effects of switching multiple times between a reference biologic and a biosimilar was evaluated in a study of 297 patients with inflammatory bowel disease treated with infliximab or two different biosimilars.[22] No association was observed in rates of persistence on medication, remission, or biochemical or fecal biomarkers for inflammation with different numbers of switches.

In the ADA-SWITCH study, 524 patients on adalimumab for inflammatory bowel disease were randomized to switch to a biosimilar (n=211) or remain on the reference drug (n=313). The rate of adalimumab discontinuation was 8% per patient-year in the group that switched vs. 7% per patient-year in the group that did not switch. Switching from adalimumab to the biosimilar was not associated with therapy discontinuation. The rate of relapse was 8% per patient-year in the group that switched vs. 6% per patient-year in the group that did not switch, an insignificant difference. Six percent of the patients had adverse events in the switching cohort vs. 5% in the non-switching cohort.

Observational data

A review of 43 cohort studies (N=7,462, 70% with Crohn's disease, 30% with ulcerative colitis) found no difference in clinical remission, adverse events or discontinuation, or safety among patients who switched from originator Remicade or Humira to their respective biosimilars.[53]

BOTTOM LINE: Evidence from randomized trials, switching studies, and cohort studies observations have demonstrated therapeutic equivalence for gastroenterological conditions between originator biologics and biosimilars.

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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This material was produced by Benjamin N. Rome, M.D., M.P.H., Assistant Professor of Medicine; Christopher Cai, M.D., Research Fellow in Medicine; Jacob S. Riegler, M.D., M.B.A., M.S.B.E., Clinical Fellow in Medicine; and Jerry Avorn, M.D., Professor of Medicine, all at Harvard Medical School; Dawn Whitney, R.N., M.S.N., Lecturer at Northeastern University and the University of Massachusetts, Boston; and Sally McNagny, M.D., M.P.H., Chief Medical Officer; Paul Fanikos, R.Ph., M.P.A./H.A., Chief Operating Officer; and Ellen Dancel, Pharm.D., M.P.H., Director of Clinical Materials Development, all at Alosa Health. Drs. Avorn, Cai, and Rome are physicians at Brigham and Women's Hospital in Boston, MA. Dr. Riegler practices at the Cambridge Health Alliance in Cambridge, MA. None of the authors accept any personal compensation from any drug company.

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