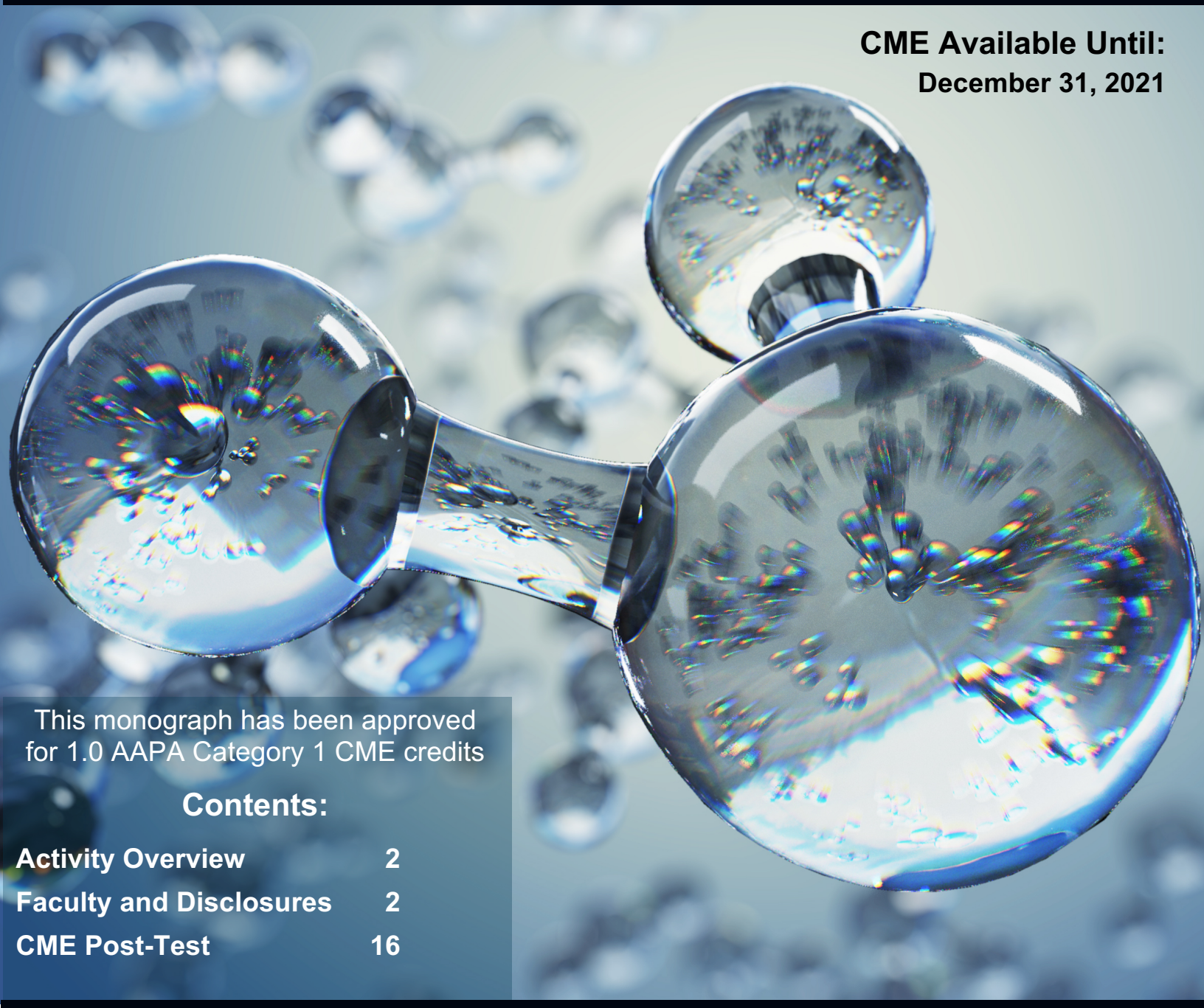
A New Era in the Treatment of Inflammatory Disorders:

Understanding the Role of Biosimilars



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ACTIVITY OVERVIEW

In 2015, the approval of the first biosimilar by the U.S. Food and Drug Administration (FDA) ushered in a new era of treatment for a range of chronic disorders. Since that time, a large number of biosimilars have been introduced, redefining the landscape of biologic therapy for patients with conditions such as inflammatory diseases. Although biosimilars offer important new treatment options, many clinicians and patients remain reluctant to use these agents due to misperceptions and lack of knowledge regarding the safety and efficacy of such treatment. As has been noted in the literature, a growing body of evidence and increasing "real-world" experience with biosimilars are likely to improve confidence in the use of these agents on the part of both healthcare providers and patients.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the PA should be better able to:

- Explain the differences between biosimilars and generics.
- Describe the process by which biosimilars are approved by the FDA.
- Apply knowledge of biosimilars to the use of these agents in patients when initiating treatment or switching from reference biologics for inflammatory conditions.
- Implement strategies for educating patients regarding biosimilar treatment options as part of shared decision-making.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The *Monograph* is designated for 1.0 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through December 31, 2021.

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Benjamin J. Smith, DMSc, PA-C, DFAAPA
Director of Didactic Education, Assistant Professor
School of Physician Assistant Practice
Florida State University College of Medicine
Tallahassee, FL
Disclosure – No relevant financial relationships to disclose

ACTIVITY PLANNERS

John Gentile, Megan Gentile, Joanne Jeffers, and Joshua Hwang, Medical Logix, LLC have no relevant financial relationships to disclose.

AAPA STAFF ACTIVITY PLANNERS

Cheryl Holmes and Daniel Pace have no relevant financial relationships to disclose.

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OVERVIEW AND IMPACT

Immune-mediated chronic inflammatory conditions include rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, and inflammatory bowel disease (IBD).[1] These conditions cause premature death, disability, and lower the quality of life in patients throughout the United States (U.S.).[2,3]

Each of these inflammatory diseases affects large numbers of Americans. The prevalence of RA in the U.S. increased from 2004 to 2014, affecting a conservative estimate of 1.28–1.36 million adults.[4] The societal costs of RA in the U.S. were $19.3 billion and $39.2 billion without and with intangible costs, respectively.[5] Similarly, based on current research, more than 8 million Americans have psoriasis.[6] Patients with psoriasis incur annual health care costs that are significantly greater than those of the general population and may amount to $135 billion annually.[7] The impact to those with IBD is also substantial. In 2015, an estimated 3 million U.S. adults reported being diagnosed with IBD, either Crohn's disease (CD) or ulcerative colitis (UC).[8] This was a large increase from the 1999 figure of 2 million adults.[9] With estimates of direct and indirect costs ranging between $14.6 and $31.6 billion in 2014, the healthcare burden associated with IBD is significant.[10]

The use of biologic drugs has proven very effective for the treatment of these conditions as they share a common pathophysiology. However, patents for many branded biologics have either expired or are set to expire over the next several years. Biologics are complicated molecules that require a significant financial commitment from the developers. This patent expiration opens the opportunity for the development of biosimilars which can provide a more financially feasible manner of providing therapy. The biosimilar industry in the U.S. has gained momentum more slowly than in Europe but is still growing.[11] Biosimilars are expected to improve access, affordability, and promote earlier use of critical therapeutic interventions for chronic inflammatory diseases. Despite available data and expert opinions, there remains considerable confusion and debate regarding the true "biosimilarity" of these agents to originator biologics. Therefore, clinical practice barriers remain associated with the use of biosimilars.[12] As more biosimilars approach FDA approval, physicians treating chronic inflammatory diseases, such as psoriasis, RA and IBD, will require education on how to overcome these barriers. The purpose of this monograph is to cover the broader landscape of biosimilar background, terminology, economic impact, currently available agents, and selected clinical trials for rheumatologic, gastrointestinal, and dermatologic indications.

BIOSIMILAR OVERVIEW

What are Biosimilars?

There is a clear need to differentiate amongst "biosimilars" and "generics". Key definitions are outlined in Table 1. Substantial differences exist between biologics (i.e., drugs produced by living systems) and traditional small-molecule drugs (i.e., chemical drugs) in terms of basic chemical structure, molecular weight, and manufacturing processes.[13] Generic small-molecule drugs can be replicated in an exact way so that they are molecularly identical to their reference drug. Biologics are complex products produced by living systems; they inherently exhibit some physiochemical differences in addition to the varying production processes that modify the products (e.g., purification methods, post-translational modification, such as glycosylation or sialylation, tertiary or quaternary structures). Therefore, a "one-size-fits-all" approach of regulatory review of a small molecule does not suit a biological drug.[14]

The Biologics Price Competition and Innovation Act (BPCIA) creates an abbreviated licensure pathway for biological products shown to be biosimilar to an FDA licensed reference product. The application for biosimilar approval must include information demonstrating that the biological product is biosimilar to a reference product (via analytical studies, animal studies and clinical studies), utilizes the same mechanism(s) of action for the proposed condition(s), has the same route of administration, dosage form, and strength, and is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent.[15]

Table 1. Understanding Biosimilar Terminology[13]

Term	Definition
Biomimetic	Human-made processes, substances, devices, or systems that imitate nature. Biologics are a type of biomimetic (e.g., monoclonal antibodies).
Biologic	A medicinal product or vaccine that consists of, or has been produced by living organisms
Biosimilar	A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (originator/reference medicinal product). A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise.

Nomenclature

The naming of biosimilars, and eventually all biologics, may cause confusion. The generic name of a biosimilar is the same as the initial generic name of the reference (originator) drug with a non-memorable four-letter suffix added to the end. For example, infliximab has one biosimilar with the brand name of Inflectra, but its non-proprietary (generic) name is infliximab-dyyb.[16] Another infliximab biosimilar, Renflexis, carries the non-proprietary name of infliximab-abda.[17] Because of this confusion, this CME article will utilize brand names as well as generic names where appropriate throughout.

The United States Food and Drug Administration (FDA) recommended this naming system in 2017 for reasons of pharmacovigilance and post-marketing surveillance.[18] It allows healthcare practitioners to clearly differentiate between these products without reference to a brand name, even though they share the same biologic basis.

Of particular confusion is that *originator* products are beginning to carry these 4-letter suffixes, as the FDA has recommended that all biological products proceed with this naming convention as well.[18] This is to better distinguish between biological medications. Tildrakizumab-asmn (Ilumya) is the first *originator* biologic, not a biosimilar, to adopt this non-proprietary naming convention in the dermatology space.[19] Other originator biologics that had been approved prior to this FDA guidance in 2017 have yet to adopt this nomenclature.

MANUFACTURING STANDARDS

Biologics are manufactured through a series of complex steps. Small changes, such as changes in culture pH and presence or absence of

various cytokines and hormones, can lead to clinically meaningful differences in the end product. Therefore, any resulting biologic will display a certain degree of heterogeneity, even between different batches of the same product.[14] In other words, they will not be 100% identical. For example, etanercept (originator) in 2010 was found to have a different quality profile than etanercept (originator) in 2009. In part, this is due to the complex relationships between primary, secondary, and tertiary structures, as well as post-translational modifications such as glycosylation.[20]

Unavoidable structural heterogeneity and differences in manufacturing have raised concerns about identity, efficacy, purity, immunogenicity, safety, and interchangeability of biosimilars.[20] The manufacturing of a biologic is often proprietary, leading to unavoidable differences between how a biosimilar and a biologic are synthesized.[21] Still, protein sequences are expected to be the same, and only small differences in the structural pattern of the molecule may be acceptable. A very intensive comparison of the structural and functional characteristics, and the product- and process-related impurities of the biosimilar and the reference product are necessary.[22,23]

Therefore, demonstrating analytically that a biosimilar is highly similar to its reference product and showing that any small differences in the molecule comparison do not have any clinically meaningful differences is a practical and appropriate policy.[14]

While the development and production of biosimilars is rigorous,[24] the above concerns motivated the FDA to release a draft guidance document on quality considerations for industry: *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry*.[25]

APPROVAL PROCESS

Clinical Trials and Data Required for Approval

The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product.[26,27]

The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product to demonstrate biosimilarity. The comparative data are generated and evaluated in a stepwise fashion:[28]

- Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- Animal studies, if necessary, including an assessment of toxicity; and
- A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD), and may also include a comparative clinical study.

Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA's previous determination of safety and effectiveness of the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.[29]

KEY CONCEPTS FOR BIOSIMILARS

Extrapolation

If the reference product is licensed to treat multiple therapeutic indications, extrapolation of indications may be possible, but must be scientifically justified. Extrapolation is the approval of a biosimilar for use in an indication held by the reference product, not directly studied in a comparative clinical trial with the biosimilar. For example, a biosimilar may be studied for RA, but may be approved for RA and IBD, which are indications of the reference product. For extrapolation to be considered by regulatory agencies such as the FDA, European Medicines Agency (EMA), and World Health Organization (WHO), biosimilarity to the reference product has to be demonstrated based on a comprehensive comparability exercise that includes efficacy and safety/immunogenicity in a key indication, and the clinically relevant mechanism of action and receptors involved in each indication has to be the same.[29]

If a proposed biosimilar is truly highly similar to the reference product, it is expected that all aspects of its therapeutic effects, including efficacy, safety, and immunogenicity, would also be similar. This principle is already applied for small-molecule generics, for which demonstration of PK bioequivalence to the reference product is usually sufficient to conclude therapeutic equivalence.[26] For biosimilars, extrapolation of indications is appropriate if there is sufficient scientific justification and based on the data from the entire development program.[30] If extrapolation of clinical data is intended, the clinical study/studies should be conducted in a therapeutic indication that is sensitive enough to detect clinically meaningful differences between the proposed biosimilar and the reference product.[30]

Extrapolation is essential to the concept of biosimilarity. The EMA states, "[t]he primary rationale for data extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency and to allocate resources to areas where studies are the most needed".[31] Replicating the efficacy and safety data of the reference product is considered scientifically nonessential and sometimes even unethical.[32]

In spite of this, some clinicians and researchers have doubts about the long-term safety and efficacy of biosimilars.[33] While they have been shown to have the same pharmacokinetic and pharmacodynamic properties and good short-term safety and efficacy data, this does not necessarily correlate with long-term outcomes: i.e., in the order of several years.[34]

Immunogenicity

All biologics, whether reference products or biosimilars, are associated with immunogenicity. The immunogenicity of an agent may differ depending on manufacturing processes and the source of the monoclonal antibodies (mouse, human, or humanized/chimeric). The FDA requires a minimum of one year of monitoring to ensure the safety of a biosimilar.[23] For drugs that are used for chronic diseases, long-term studies analyze their immunogenicity. Trials typically assess for the development of antidrug antibodies (ADAs), comparing the reference product to the biosimilar. ADAs may be responsible for certain adverse effects or later diminished efficacy of the medication.[23]

Clinicians are particularly concerned with the potential for increased immunogenicity when switching between biologics/biosimilars, once

or several times. Although, trials studying switching so far have not demonstrated increased immunogenicity when comparing switches with biosimilars compared with reference products.[35]

Dosing

The prescribing of biosimilars follows the same route of administration, same dose, and same potency of the reference product. Occasionally there may be a difference in the *dosage form*. For example, the first biosimilar approved in the United States, filgrastim-sndz (Zarxio) is available in pre-filled syringes, whereas the reference product is available in prefilled syringes and in vials.[21]

Interchangeability

In addition to the data required for approving a biosimilar, an application for an *interchangeable* designation must also include information or data demonstrating that (1) the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient; and (2) for a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.[36]

This FDA guidance describing the criteria for interchangeability was released in early 2017.[36] As such, biosimilars approved before the release of this were not required to provide this level of data to prove their interchangeability. As of 2020, there are no biosimilars with the interchangeable designation.[37] Pharmacists may substitute reference products for interchangeable biosimilars, subject to state-level policies, when an agent receives this interchangeable designation.[38]

PRACTICAL ISSUES IN SWITCHING TO BIOSIMILARS

Often biosimilars are approved for use in all of the indications of the reference biologic. However, due to patent exclusivity agreements or patent litigation, each biosimilar agent may not be approved for all indications as the originator reference product. As such, clinicians must be mindful of the approved indications of the biosimilar. See Table 2 for a listing of inflammatory disease indications of selected biosimilars.

Decisions to switch biologic treatments should be made by the clinician, backed by scientific data, and through shared decision making with the patient. As clinical situations may differ, these decisions should be tailored to the individual patient. Though biosimilars share the same base molecule, switching data is not necessarily transferable between biosimilars. Regarding adverse event profiles, while approved biosimilars are deemed to be bioequivalent to their reference biologics, one should consider potential differences in AE profiles. Current randomized trials and real-world data for biosimilars may be underpowered to reveal rare AEs.[39]

Patient factors must also be considered, such as their ability to implement different instructions for mode of administration, as with a different injection device for example.[40] Of course, one must weigh patient preference and attempt to diminish potential nocebo effects of switching.[41]

Some trials have described greater reporting of adverse events and discontinuations due to the nocebo effect.[40–42] The nocebo effect may result in the patient and/or clinician concluding that a switch from reference product to biosimilar is less effective or may result in adverse events.[43] Groups such as Kaiser Health Plans have worked to reduce this nocebo effect by increasing clinician buy-in. This is discussed further in the *Economic Benefits* section.

To this end, clinicians have made recommendations regarding switching between biologic reference products and biosimilars:[40]

(1) The decision to switch should be based on scientifically sound (including real-world) data.

(2) Switching between reference biologic and biosimilar products, or between different biosimilar products, should remain a clinical decision to be made by the treating clinician on an individual patient basis with patient awareness.

(3) Switching data from one biologic molecule should not be used to inform switching decisions between other biologic/biosimilar treatments.

(4) Automatic substitution at the pharmacy level should not take place, as this decision would not be made by the treating physician.

(5) Patients should be closely followed post-switching to monitor for AEs; data should be made available for national registries that report into large pharmacovigilance databases.

(6) The decision to switch patients from a reference product to its biosimilar should be made on a case-by-case basis depending on the underlying disease, patient characteristics and comorbidities, type of reference drug, and patient willingness to switch.

ECONOMIC BENEFITS

Research by the RAND Corporation estimates that biosimilars could save the U.S. healthcare system $54 billion over a ten-year period.[11] A study from Johns Hopkins to the U.S. Department of Labor reported that an infliximab biosimilar was 68% of the price of the reference product, with patients paying 12% less out-of-pocket. The researchers reported that companies with their own insurance may have potentially saved $407 million to $1.4 billion in 2018 had they switched from reference infliximab and filgrastim to biosimilars. The potential Medicare savings were estimated at nearly $300 million given the same switch[44]

The potential for savings is massive, due to the United States' large spending on biologics. At $120 billion, biologics represent more than one-third of net drug spending (37%), though, by number, they only represent 2% of prescriptions written. From 2014 to 2018, biologic medications represent 93% of the overall growth in total medication spending.[45] Still, however, biosimilars have not yet reduced U.S. healthcare spending meaningfully.

Biosimilar uptake in the U.S. has been limited by pricing and reimbursement models tied to its healthcare system. By way of example, infliximab remains on the formulary for most major payers despite the presence of its biosimilar that is offered at a 15% wholesale discount.[33] In addition, because no automated substitution between a biologic and a biosimilar (contrary to generics) is currently allowed, coupled with more emerging new biologics that have a long patent life, wider utilization of biosimilars in U.S. markets remains speculative, affecting accurate cost reduction calculations. Cost implications can also be affected by reimbursement programs and/or rebate agreements between manufacturers and payers, in which incentives might be provided for allowing an expensive biologic versus a biosimilar.[46–48]

Public and private organizations have made strides in improving cost structures and the use of biosimilars, however. The Veterans' Affairs (VA) Healthcare System is the largest single healthcare system in the United States. As such, it can negotiate price and manage contracts, unlike Medicare. For largely financial reasons, it has led the switch to

biosimilars.[49,50] Through the same tactics, researchers estimate that Medicare could have saved $14.4 billion in 2015.[51]

Similarly, Kaiser Health Plans have successfully increased use of biosimilars. The initial motivation for this was to drive down costs. One major tactic was to decline rebates; this pushed the balance towards biosimilar cost savings. To address possible nocebo effects, Kaiser Health proactively addressed clinician switching concerns. They involved stakeholder clinicians using evidence-based approaches to switching policy decisions. As well, to address the concerns of certain GI clinicians regarding the safety of infliximab biosimilars, Kaiser Health created a registry to aggregate and report issues. Currently, there have be no reported differences in safety or efficacy, as demonstrated by a 54-week study in patients with IBD switching from infliximab (originator) to biosimilar infliximab-dyyb (Inflectra).[52] Regarding the success of this switching program, 95% of patients receiving infliximab were switched to infliximab-dyyb. From 2017, at program launch, to late 2019, Kaiser Health has saved approximately $200 million.[53]

To promote biosimilar competition, in 2018 the FDA created the Biosimilars Action Plan (BAP). The BAP aims to add to the existing legislation on biologic development and patent protection while still positioning biosimilars to save healthcare dollars: "One of FDA's less appreciated roles is to take responsibility for implementing laws intended to strike a balance between encouraging and rewarding innovation in drug development and facilitating robust and timely market competition".[54]

AVAILABLE BIOLOGICS IN RHEUMATOLOGY, GASTROENTEROLOGY, AND DERMATOLOGY

While several biosimilars for agents used in inflammatory diseases have been approved by the FDA, only a small fraction of these are currently marketed in the U.S. due to issues of patent litigation or decisions by the manufacturer not to market the agent.[55] This section will focus on those currently marketed in the U.S. or those that will likely be marketed in the next few years. See Table 2 for an overview of the currently and soon-to-be available biosimilars for rheumatologic, gastroenterological, and dermatological indications.

Three infliximab biosimilars are currently available to prescribe: infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), and infliximab-axxq (Avsola). Two rituximab biosimilars are available: rituximab-abbs (Truxima) and rituximab-pvvr (Ruxience). Several biosimilars of adalimumab have been approved for use by the FDA, notably adalimumab-bwwd (Hadlima), adalimumab-adaz (Hyrimoz), adalimumab-adbm (Cyltezo), and adalimumab-atto (Amjevita). However, due to patent litigation issues, these adalimumab biosimilars will not be marketed in the U.S. until 2023. Biosimilars of etanercept have been approved as well, including etanercept-szzs (Erelzi) and etanercept-ykro (Eticovo), though recent appeals by biosimilar manufactures were not successful and these will not be available until 2029.[55]

For the majority of the biosimilars approved and currently marketed, their indications match those of their reference product. The notable exception is rituximab-pvvr (Ruxience), which is not indicated for rheumatoid arthritis. This is potentially due to a settlement agreement between Pfizer and Genentech for the use of rituximab for certain indications.[56]

Table 2: Currently and soon-to-be available biosimilars indicated for inflammatory disease

Biosimilar	Rheumatologic indications	Gastrointestinal indications	Dermatologic indications	Currently available
Infliximab biosimilars				
Renflexis (SB2, infliximab-abda)[17]	Rheumatoid arthritis (in combination with methotrexate); ankylosing spondylitis; psoriatic arthritis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	Yes
Inflectra (CT-P13, infliximab-dyyb)[16]	Rheumatoid arthritis (in combination with methotrexate); ankylosing spondylitis; psoriatic arthritis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	Yes
Avsola (ABP-710, infliximab-axxq)[65]	Rheumatoid arthritis (in combination with methotrexate); ankylosing spondylitis; psoriatic arthritis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	Yes
Rituximab biosimilars				
Truxima (CT-P10, rituximab-abbs)[66]	Rheumatoid arthritis (in combination with methotrexate); granulomatosis with polyangiitis; microscopic polyangiitis (in combination with glucocorticoids)	--	--	Yes
Ruxience (PF-05280586, rituximab-pvvr)[67]	Granulomatosis with polyangiitis; microscopic polyangiitis (in combination with glucocorticoids)	--	--	Yes
Adalimumab biosimilars				
Cyltezo (BI-695501, adalimumab-adbm)[68]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	No (2023)
Amjevita (ABP-501, adalimumab-atto)[69]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	No (2023)
Hyrimoz (GP2017, adalimumab-adaz)[70]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	No (2023)
Hadlima (SB5, adalimumab-bwwd)[71]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	Crohn's disease; ulcerative colitis	Plaque psoriasis; psoriatic arthritis	No (2023)
Etanercept biosimilars				
Eticovo (SB4, etanercept-ykro)[72]	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	--	Plaque psoriasis; psoriatic arthritis	No (2029)
Erelzi (GP2015, etanercept-szzs)[73]	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis	--	Plaque psoriasis; psoriatic arthritis	No (2029)

CLINICAL TRIAL DATA

Biosimilar clinical trials do not aim to replicate all of the pivotal clinical trials that originally proved efficacy and safety.[27] Instead, the biosimilar approval pathway uses smaller trials with sensitive endpoints in sensitive populations to prove that the biosimilar is not meaningfully different, i.e., that it is equivalent or noninferior to the reference product.[29] The prescribing information for biosimilars often refers to the reference product's data when covering efficacy, safety, and immunogenicity rates.

Often the initial approval of biosimilars comes from studies for one disease or family of diseases (e.g., rheumatoid arthritis), but due to the principle bioequivalence they are approved for the remaining indications of the reference product (e.g., IBD).

These trials are summarized in Table 3. As these products are more widely used in Europe, real-world data is now becoming available for other indications other than the original bioequivalence studies. Still however, there is a need for data for these other indications, especially dermatologic indications.

Broadly speaking the bioequivalence trials and emerging real-world data have shown similar results between biosimilars and originator products: similar efficacy (within 15% of a chosen objective marker of disease), no significant differences in adverse event profile, or immunogenicity. Similarly, extension trials have shown similar results.

Table 3: Trial design of selected biosimilar trials

Trial (biosimilar)	*Trial design*	*Population and intervention (N)*	*Outcome measure*
Rheumatologic indications			
NCT01936181 (Renflexis, SB2, infliximab-abda)[74]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe RA despite MTX therapy: received SB2 (n=291) or INF (n=293)	**1° outcome**: ACR20 response at week 30; **2° outcomes**: safety, immunogenicity (ADA incidence), and PK
PLANETRA (Inflectra, CT-P13, infliximab-dyyb)[75]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Active RA despite MTX: received CT-P13 (n=302) or INF (n=304) with MTX and folic acid	**1° outcome**: ACR20 response at week 30; **2° outcomes**: safety, immunogenicity (ADA incidence), and PK
PLANETAS (Inflectra, CT-P13, infliximab-dyyb)[76]	Phase I, randomized, double-blind, multicenter, multinational, parallel-group	Active AS: received CT-P13 (n=125) or INF (n=125)	**1° outcome**: PK endpoints (AUC at steady state, steady state C_{max}) between weeks 22 and 30); **2° outcomes**: other PK endpoints, efficacy endpoints (including ASA20 and ASA40), and safety
NCT02937701 (Avsola, ABP-710, infliximab-axxq)[77,78]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe RA despite MTX: received ABP-710 (n=279) or INF (n=279)	**1° outcome:** ACR20 at week 22; **2° outcomes**: DAS28-CRP, ACR20/50/70, safety, immunogenicity
NCT02149121 (Truxima, CT-P10, rituximab-abbs)[79]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Adults with active RA: received CT-P10 (n=161), U.S.-sourced RTX (n=151), or EU-sourced RTX (n=60)	**1° outcome**: PK endpoints (AUC_{0-last}, $AUC_{0-\infty}$, and C_{max} after two infusions); 1° efficacy endpoint: change from baseline to week 24 in DAS28-CRP; **2° outcome**: PD, immunogenicity, and safety
REFLECTIONS B328-01 (Ruxience, PF-05280586, rituximab-pvvr)[80]	Phase I, randomized, double-blind, multicenter, multinational, parallel-group	Active RA on MTX with inadequate response to ≥1 anti-TNF (n=198): received PF-05280586, EU-sourced RTX or U.S.-sourced RTX	**1° outcome**: PK properties (C_{max}, AUC_T, $AUC_{0-\infty}$ and $AUC_{2\text{-week}}$); **2° outcome**: PD, immunogenicity, safety, and tolerability
VOLTAIRE-RA (Cyltezo, BI-695501, adalimumab-adbm)[81]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Active RA on stable MTX: received BI-695501 (n=324) or adalimumab (n=321)	**1° outcome**: ACR20 response at weeks 12 and 24; **2° outcomes**: DAS28-ESR, ACR20/40/70 at 48 weeks, safety, tolerability, and immunogenicity
NCT01970475 (Amjevita, ABP-501, adalimumab-atto)[82]	Phase III, randomized, double-blind, multicenter, multinational	Moderate-to-severe active RA despite MTX: received ABP-501 (n=264) or adalimumab (n=261)	**1° outcome**: risk ratio of ACR20 between groups at week 24; **2° outcomes**: ACR50/70, DAS28-CRP, safety, tolerability, and immunogenicity (ADA incidence)
ADMYRA (Hyrimoz, GP2017, adalimumab-adaz)[83]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe RA despite DMARDs: received GP2017 (n=140) or adalimumab (n=144)	**1° outcome**: DAS28-CRP at week 12; **2° outcomes**: mean changes in DAS28-CRP, EULAR response, safety, and immunogenicity (ADA incidence)
NCT02167139 (Hadlima, SB5, adalimumab-bwwd)[84]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe active RA despite MTX: received SB5 (n=269) or adalimumab (n=273)	**1° outcome**: ACR20 response at week 24; **2° outcomes**: ACR50/70 response, DAS28-ESR, PK, safety, and immunogenicity (ADA incidence)
NCT01895309 (Eticovo, SB4, etanercept-ykro)[85]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe active RA despite MTX: received SB4 (n=299) or etanercept (n=297)	**1° outcome**: ACR20 response at week 24; **2° outcomes**: ACR50/70 response, DAS28-ESR, PK, safety, and immunogenicity (ADA incidence)
EQUIRA (Erelzi, GP2015, etanercept-szzs)[86]	Phase III, randomized, double-blind, multicenter, multinational, parallel-group	Moderate-to-severe RA despite DMARDs: received GP2015 (n=186) or etanercept (n=190)	**1° outcome**: DAS28-CRP at week 24; **2° outcomes**: mean changes in DAS28-CRP, EULAR response, ACR20/50/70 response, safety, and immunogenicity (ADA incidence)

Trial (biosimilar)	*Trial design*	*Population and intervention (N)*	*Outcome measure*
Gastroenterology indications			
SPOSIB (Renflexis, SB2, infliximab-abda)[87]	Observational, prospective, cohort, multicenter	CD (n=136) and UC (n=140); 46.0% anti-TNF–naïve, 23.5% INF-naïve (but anti-TNF exposed); 6.2% switched from INF to SB2, 15.6% switched from CT-P13 to SB2, 8.7% multiply switched	**1° outcome**: safety (SAEs); **2° outcomes**: effectiveness as % achieving steroid-free clinical remission (Harvey-Bradshaw Index <5 for CD and partial Mayo score <2 for UC without steroids use) and partial response after 8 and 52 weeks; treatment persistence (similar safety and efficacy between patients undergoing single or multiple switches)
PROSIT-BIO (Inflectra, CT-P13, infliximab-dyyb)[88]	Observational, prospective, cohort, multicenter	CD (n=313) and UC (n=234) patients naive to anti-TNF, previously treated with anti-TNF, or switched from INF	**1° outcome**: safety (SAE); **2° outcomes**: efficacy (clinical remission/response and treatment persistency) and immunogenicity (occurrence of infusion reactions and loss of response)
VOLTAIRE-CD (Cyltezo, BI-695501, adalimumab-adbm)[89]	Phase III, randomized, double-blind, multicenter	Active CD: received BI-695501 (n=68) or adalimumab (n=75)	**1° outcome**: % of patients with clinical response (CDAI decrease ≥70 vs baseline) at Week 4; **2° outcomes**: % with clinical response at Week 24, clinical remission (CDAI <150) at Week 24, AEs, SAEs, and AEs of special interest
Dermatology indications			
NCT01970488 (Amjevita, ABP-501, adalimumab-atto)[90]	Phase III, randomized, double-blind, multicenter, multinational	Moderate-to-severe psoriasis: received ABP-501 (n=174) or adalimumab (n=173); re-randomized at week 16	**1° outcome**: % improvement in PASI score from baseline to week 16; **2° outcomes**: PASI50/75, static PGA response, and mean change in BSA affected; safety (TEAEs, SAEs, immunogenicity [ADA])
Psobiosimilars registry (Inflectra, CT-P13, infliximab-dyyb)[91]	Observational, retrospective, registry	Psoriasis (n=204) patients taking CT-P13: switched from INF to the biosimilar, or naive to INF	PASI scores; AEs

ACR20, American College of Rheumatology 20% response; ADA, antidrug antibodies; AE, adverse event; AS, ankylosing spondylitis; ASA20/40, Assessment in Ankylosing Spondylitis International Working Group criteria 20% and 40% improvement; AUC, area under the concentration-time curve; BSA, body surface area; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; C_{max}, maximum concentration; DAS28-CRP, Disease Activity Score using 28 joints-C-reactive protein; DAS28-ESR, Disease Activity Score using 28 joints-erythrocyte sedimentation rate; EU, European Union; EULAR, European League Against Rheumatism criteria; INF, infliximab; MTX, methotrexate; PASI, psoriasis area and severity index; PD, pharmacodynamics; PGA, Physician's Global Assessment; PK, pharmacokinetics; RA, rheumatoid arthritis; RTX, rituximab; SAE; serious adverse event; TEAE, treatment-emergent adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis; U.S., United States

NOR-SWITCH TRIAL

Among these trials, the NOR-SWITCH trial bears highlighting. The NOR-SWITCH study was commissioned by the government of Norway to compare the efficacy, safety, and immunogenicity of infliximab-dyyb (Inflectra) with the originator infliximab.[57] The study was a randomized, non-inferiority, double-blind, phase IV trial. Adult patients being treated with infliximab (originator), on a stable dose, for various inflammatory indications were enrolled. They were randomized to receive either infliximab originator or biosimilar infliximab-dyyb, with dosage maintained. The study was conducted at sites across Norway. The primary endpoint was disease worsening during 52-week follow-up. A non-inferiority margin of 15% was the pre-established threshold.[57]

Of the 481 patients included in the full analysis set, 155 (32%) patients had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis.[57]

The rate of disease worsening was similar between groups and within the 15% margin: 26% patients in the infliximab (originator) group and 30% patients in the infliximab-dyyb group. Adverse event rates were similar between groups as well: serious adverse event rates were 10% for infliximab (originator) compared with 9% for infliximab-dyyb; overall adverse event rates were 70% compared with 68%; and adverse events leading to treatment discontinuation, 4% versus 3%, respectively.[57]

Risk differences for the primary endpoint were analyzed in an exploratory analysis for the individual conditions: Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and psoriasis. The researchers found that the spondyloarthritis subgroup was inferior, while the other diseases were all non-inferior. It is important to note; however, that the numbers in each subgroup were small (17 versus 14 in the spondyloarthritis subgroup) and that this was an exploratory analysis.[57]

Immunogenicity Data

Though some clinicians are concerned that biosimilars may result in increased immunogenicity, current research does not bear this out. Overall, bioequivalence studies have found similar rates of ADA formation between originator and matched biosimilars. In a large systematic review of 90 studies (14,225 patients) on biologic and biosimilar switching, researchers found that the safety profiles after switching from originator products to biosimilars were similar to safety profiles with continued use of originator products themselves.[35] Specifically, three large trials where patients were switched multiple times did not demonstrate significant differences in efficacy or safety when the originator and biosimilar medications were compared.[58–60] Two papers reported loss of efficacy and/or increased discontinuation rates,[61,62] though others attribute this to a nocebo effect.[63]

One trial among the trials analyzed bears highlighting. Researchers explored the cross-reactivity of ADA in subjects exposed to infliximab originator, infliximab-dyyb (Inflectra), or infliximab-abda (Renflexis).[64] They found that all antibodies cross-reacted with any type of infliximab molecule. More specifically, (1) antibodies developed against the originator product cross-reacted with biosimilars infliximab-dyyb or infliximab-abda, and (2) antibodies developed in patients exposed to infliximab-dyyb also identically cross-reacted with originator inflixmab and biosimilar infliximab-abda. This matched cross-reactivity implies that switches between these products have very similar immunogenicity profiles.

CONCLUSION

As patents for biologics expire, more and more biosimilar medications will enter the U.S. market. As such, clinicians will require a deeper knowledge of biosimilars and their background. The potential benefit offered by biosimilars is massive both in terms of cost-savings and access. While the pathway to biosimilar approval is abbreviated compared with the approval of an originator biologic, the research required must still be rigorous. Key to these data are evidence of efficacy, with objective markers of disease severity, and safety, through adverse event and immunogenicity tracking. Thus far, the uptake of biosimilars has been limited due to the peculiarities of the U.S. healthcare system and payer–insurance mechanics. Still, however, public and private healthcare systems are making efforts to reduce expenses with biosimilars. The FDA has also created the Biosimilars Action Plan in order to encourage competition. Currently, only infliximab and rituximab biosimilars are available in the U.S. for inflammatory disease indications: infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), infliximab-axxq (Avsola), rituximab-abbs (Truxima), and rituximab-pvvr (Ruxience). Adalimumab biosimilars will be available in 2023 and etanercept biosimilars will be available in 2029. Both have been delayed because of patient litigation. The original bioequivalence studies leading to biosimilar approvals and now increasing real-world evidence are demonstrating that biosimilars, compared with their reference medications, are similarly effective and safe. Continued surveillance and research will demonstrate the longer-term safety and efficacy profile of these agents.

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CME POST-TEST: Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central. See page 2 for further information.

Question #1

A biosimilar approved by the FDA may be substituted without the intervention of the healthcare provider who prescribed the reference product under what circumstances?

A. All biosimilars approved by the FDA may be substituted for approved indications
B. If state substitution laws allow
C. If approved as interchangeable by the FDA and allowed by state substitution laws
D. Substitution rules vary depending on biosimilar therapeutic class

Question #2

Which biological products are subject to variability in the manufacturing process?

A. Reference biologics
B. Biosimilars
C. Both reference biologics and biosimilars
D. Neither reference biologics nor biosimilars

Question #3

Which statement describes the FDA draft guidance for non-proprietary naming of biological products?

A. Same name as the reference product
B. International non-proprietary name (INN) of reference product + unique four-letter suffix
C. Unique four-letter prefix + international non-proprietary name (INN) of reference product
D. Completely different name

Question #4

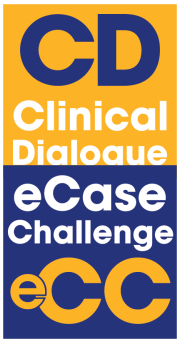
Which statement best describes the European biosimilar experience?

A. Increased side effects reported for biosimilars compared with reference agents
B. Dose reduction is possible for some approved biosimilars due to increased potency
C. Uptake for biosimilars for rheumatologic conditions is quite low
D. Safety, efficacy, and immunogenicity consistent with experience with reference biologics

Question #5

Which statement best describes the use of adalimumab biosimilars?

A. Adalimumab biosimilars are not yet available to prescribe in the United States
B. Adalimumab biosimilars have not been approved by the FDA
C. Adalimumab biosimilars have different pharmacokinetic and safety profiles compared to reference adalimumab
D. Adalimumab biosimilars have exactly the same manufacturing process as reference adalimumab



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