Clinical Practice Guideline

Biosimilars in Rheumatology

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Abbreviations

ACA	Patient Protection and Affordable Care Act
ACR	American College of Rheumatology
AS	Ankylosing spondylitis
BPCIA	Biologics Price Competition and Innovation Act
bsDMARDs	Biosimilar disease-modifying antirheumatic drugs
DMARD(s)	Disease-modifying antirheumatic drug(s)
DNA	Deoxynucleic acid
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IMS Health	Institute for Health Informatics
IV	Intravenous
mAbs	Monoclonal antibodies
MTX	Methotrexate
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
TNF	Tumor necrosis factor
SQ	Subcutaneous
UK	United Kingdom
US	United States

Introduction

The introduction of biologic medications over the last three decades has been life-changing for many patients suffering with a wide variety of diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA), systemic lupus erythematosus, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, hematologic cytopenias, diabetes, hepatitis C, and cancer.

Biologics are large molecules when compared to most standard drugs, which are categorized as small molecules. When used appropriately, biologics can very effectively slow the progression of rheumatologic disorders, improving a patient's quality of life and preventing disabilities.

However, these drugs are very expensive so-called "specialty drugs". Although there is no standard definition, in general, medications are considered to be specialty drugs when the annual cost of treatment is very high. For example, Medicare considers a medication to be a specialty drug when the monthly cost is $600 or more.[1] In some cases, the cost of a specialty drug can exceed $100,000 per year.[2] Other parameters used to place a medication into the specialty-drug group include but are not limited to the following:[3, 4]

- Treats an unusual or rare condition
- Needs special handling (i.e. refrigeration during shipping and storage)
- Uses a limited distribution network
- Requires tight quality control and ongoing re-evaluation of efficacy, safety, and adverse immune response
- Costs >$600/month
- Prescribed by a specialist
- May be associated with a patient payment assistance program
- Requires close patient monitoring

Because these medications are so costly, health plans often impose cost sharing rules, making some specialty drugs unaffordable to patients.

Only 10 years ago, most specialty drugs were injectables, but currently the list also includes oral and inhaled drugs. According to the American Journal of Managed Care,[3] only ten specialty drugs were available in the United States (US) in 1990 and by 2012, there were close to 300, with an estimated 500 specialty drugs in existence in 2016.[5] Furthermore, nearly half of the drugs in the current drug pipeline will potentially fall into the specialty drug category.[3] In 2014, specialty drugs accounted for only 1% of the prescriptions written in the US, but for 32% of all drug spending.[6] According to the Institute for Health Informatics (IMS Health), drug spending in the US reached $425 billion in 2015; specialty drugs accounted for $150.8 billion in that year or 35.5% of the total drug spend in the US.[7] In 2016, there was an increase in total prescription spending of 5.8% compared with 2015 with the greatest drug spend for the biologic adalimumab at $13.590 billion, an increase of 27.6% over 2015.[8] Biologics also accounted for the fourth and fifth greatest spends; etanercept at $7.362 billion, an 11.2% increase over 2015 and infliximab at

$5.310 billion, a 6.6% increase over 2015, respectively.[8] In 2017, the IQVIA Institute (formerly IMS Health) reported that the spend for specialty drugs was nearly half of the total US medication spend.[9]

Most drugs used in the US are not biologics. These traditional drugs (also known as small molecule or chemical drugs) have a specific chemical formula that can be reproduced by "combining specific chemical ingredients in an ordered process".[10] Copies of these drugs are known as "generics", and they are identical to the original drug. According to the Food and Drug Administration (FDA), generics must be identical copies of the brand-name drug "in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use".[11] In addition, generics are less costly than brand-name drugs. The Congressional Budget Office estimates that generics save patients $8 to $10 billion annually.[12]

According to the American College of Rheumatology (ACR), the most common biologics used to treat rheumatologic disorders are monoclonal antibodies (mAbs),[13] which can be 200–1000 times the size of traditional small-molecule drugs. Biologics are frequently produced using recombinant deoxyribonucleic acid (DNA) technology. The genetically engineered cells from which they are produced are capable of manufacturing biologic medications that are "therapeutic proteins" or "mAbs".[14]

Biologics also include vaccines, blood products, gene and cell therapies, as well as therapeutic proteins.

Unlike generic drugs, manufacturers of biosimilars do not have access to the brand-name manufacturer's process; they must reverse engineer the biosimilar from the reference drug. As a result, the biosimilar is not, nor is it expected to be, an identical copy of the reference drug.

The complex process of manufacturing biologic drugs is beyond the scope of this guideline. The ACR, in its 2015 Position Statement on Biologics (Page 2), has summarized the manufacturing process as follows:[13]

> *Production of these agents requires highly technical processes and reagents that must be exquisitely controlled and monitored. Generation of a recombinant biologic starts with a rationally designed DNA sequence (a gene) that must be expressed in a host system. Host systems used to produce biologics include bacteria, yeast, insect cells, transgenic animals, and human or other mammalian cell lines. Targeted DNA sequences are transcribed and then translated by the host cell into peptides that fold and combine into proteins with highly complex tertiary and quaternary structures. This process is accompanied by posttranslational modifications of the proteins (including, but not limited to, glycosylation, oxidation and phosphorylation) that affect their efficacy, stability and immunogenicity.*
>
> *The host cell and the conditions under which the proteins are generated and purified (especially temperature, pH, cell density, oxygenation and osmolality) can have dramatic effects on posttranslational modifications and the purity of the final product. This impacts the efficacy, immunogenicity and safety of the drug. Finally, precipitation and aggregation of protein complexes that can take place during the manufacturing and storage of these agents further impacts their stability, efficacy and tolerability. These complexities necessitate the tremendous care (especially with respect to temperature, mechanical agitation and proper reconstitution) that must be taken to ensure proper delivery and administration of these drugs to patients.*

As can be seen from the above ACR statements, even minor changes in the production environment can result in significant changes in "structure, stability or other quality aspects" of these drugs, which in turn, can alter the drug with respect to its stability, safety, efficacy, and immunogenicity. These changes can be seen in both the reference drugs and biosimilars, and occur "during production and storage as well as within patients after administration".[15]

The FDA Approval Process

The wide availability and variety of generics has had a dramatic impact on the cost of small-molecule drugs since 1984. According to a working paper from the National Bureau of Economic Research,[16] generics made up 74.5% of the small-molecule retail prescriptions in the US in 2009. This rose to 90% in 2017 and represented only 23% of the total cost of small molecule drugs.[17]

The FDA process for the approval of small-molecule generic drugs is relatively simple, inexpensive, and quick when compared to the approval process for biosimilars. The law governing the approval process for generics was changed in 1984 by the Waxman-Hatch Act. Manufacturers of generic drugs are now only required to demonstrate that their product is bioequivalent to and can be safely substituted for the brandname drug. In addition, they must be able to document that the active ingredient in the generic is identical to the one in the brand-name drug. The FDA approval of a generic is usually very fast once the patent on the brand-name drug expires. According to the FDA, the price of generics decreases with the number of choices for a given brand-name drug on the market, resulting in overall decreased costs for prescription drugs.[18]

Biosimilars (sometimes referred to as follow-on biologics) are similar but not exact copies of the reference (brand-name) drug. Recently, interest in biosimilars has been increasing as patents for brand-name reference drugs expire and it is hoped that the use of biosimilars will result in reduced overall spending on biologics.

A few years ago, Congress became concerned about the rapidly rising costs of biologic medications. To encourage the availability of more cost-effective treatments, they created a new, hopefully faster, approval process for biosimilars. The Patient Protection and Affordable Care Act (ACA), which became law in 2010, includes a section called the Biologics Price Competition and Innovation Act (BPCIA). This section of the law describes an abbreviated process for FDA approval of biosimilar drugs, which allows for minor differences in inactive ingredients in the biosimilar when compared to the brand-name biologic or reference drug. It also contains a section that allows for the possibility that biosimilars might be interchangeable with the brand-name reference drug. According to this law, "An *interchangeable* biological product is biosimilar to an FDA-approved product and meets additional standards for interchangeability" and "An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product."[19]

At first glance, the provisions of this section (BPCIA) of the ACA appear to be similar to the 1984 legislation for the expedited approval of generics (Waxman-Hatch Act); however, there are some differences. Unlike the approval process for generics, approval of biosimilars requires preclinical and clinical data that is more

extensive than just the demonstration of structural equivalence and bioequivalence. Manufacturers of biosimilars must submit data that include structural and functional assays, a "toxicity assessment" as well as "immunogenicity, pharmacokinetics and/or pharmacodynamics" studies (Page 35).[20] At least one clinical study demonstrating noninferiority between the originator and the biosimilar in at least one disease state in which the originator is FDA approved must be submitted.

The FDA released final versions of guidance documents for approval of biosimilars in 2015. These documents discuss the scientific considerations in demonstrating biosimilarity, provide quality requirements for biosimilars, and include questions and answers concerning the implementation of the BPCIA of 2009.[21] It also provides guidance for extrapolation of indications. This means that data from a clinical trial of a biosimilar conducted in one disease may be used to support approval for additional indications for which the reference product is already approved. The issue of extrapolation of indications is also briefly discussed in a guidance document released by the FDA in 2019, which states that the FDA will require that "*The sponsor provide sufficient scientific justification for extrapolating data and information to support a determination of interchangeability for each indication of use for which licensure as an interchangeable product is sought*" (Page 15).[22]

The cost of developing and getting approval for biosimilar drugs is significantly greater than that for generics. Although biosimilars are expected to be expensive, it is thought that they may be as much as 15% to 30% lower in cost than their reference drugs.

Often rheumatologists and their patients struggle to find the right drug or drug combination to achieve the best possible results. Achieving remission or low disease activity in patients with RA, PsA, or spondyloarthritis is a painstaking task often marked by trial and error. Not every patient with the same disease activity responds to the same biologic. There are even differences in the response of different patients to different reference biologics in the same class. Once in remission, or as close to it as possible, it is important to maintain that clinical response level and avoid and/or delay the onset of flares. Rheumatologists might be reluctant to change medications in patients with stable disease, because biosimilars are not exact copies of the reference drug and it is difficult to predict if a particular patient will respond in the same manner as he/she has to a reference drug.[13]

Switching and Substitution (Interchangeability)

There is a significant difference between "switching" from one biopharmaceutical to another (including switching from a reference drug to a biosimilar) and substitution (interchangeability) of biopharmaceuticals. As mentioned above, rheumatologists may be reluctant to change or switch medications once they have found a drug that results in the desired clinical response. However, if there were adequate clinical studies demonstrating that switching from one drug to another did not decrease efficacy and had a similar tolerability profile, a rheumatologist might consider whether a change or switch is appropriate for their patient. A rheumatologist may recommend switching medications for several reasons, including:

- Decreasing patient out-of-pocket cost

- Drug toxicity
- Change in payer formulary
- Failure to respond
- Development of anti-drug antibodies

A drug cannot be switched or considered to be interchangeable without FDA approval of interchangeability. Currently, there are no biosimilars that are approved as interchangeable in the US.

In 2019, the FDA released guidance for industry to assist companies who wish to submit an application for approval of a biosimilar as interchangeable with a reference drug.[22] However, it should be noted that the guidance offered in this document is not a requirement for manufacturers but rather suggestions or recommendations from the FDA. It is possible that future legislation or FDA policy may require manufacturers to demonstrate specific data for a drug to be licensed as interchangeable. The current document describes the scientific data that the FDA suggests is needed to label a biosimilar as interchangeable with a reference drug. These include the following (Pages 2–3):[22]

- *Data and information needed to support a demonstration of interchangeability*
- *Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability*
- *Considerations regarding the comparator product in a switching study or studies*
- *Abbreviated considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products*

In some states, if a biosimilar drug is labelled interchangeable then a pharmacist may substitute it for the reference drug without the approval of the prescribing provider. In 2018, the ACR issued a Position Statement on Biosimilars in which they opposed this practice even if permitted by state regulations.[23] The ACR believes that only the prescribing provider should determine if a biosimilar drug should be substituted for the prescribed reference biologic for an individual patient.

On May 10, 2019, the FDA published a statement from the acting FDA Commissioner Ned Sharpless, M.D., regarding FDA policy advancements to help bring interchangeable biosimilars to market.[24] The statement describes the "pathway for "*interchangeable biologics, which may be substituted without the involvement of the prescriber, similar to how generic drugs are routinely substituted for brand name drugs when they are prescribed for patients*". Although the 2019 FDA guidance document[22] indicates that the information listed, which may be submitted with an application to approve a biosimilar as interchangeable are only suggestions or recommendations, it is clear from Dr. Sharpless' statement that the clinical and scientific information described in the guidance document must accompany an application for approval of a biosimilar as interchangeable with a reference drug.

A 2007 publication in *Arthritis and Rheumatism* describes the experience of 6739 patients with RA treated with anti-tumor necrosis factor (TNFi) medications.[25] Over approximately 15 months, 1864 patients discontinued the first drug; 841 because it was ineffective and 1023 due to adverse events. Subsequently, 503 patients of the 841 and 353 patients of the 1023 were switched to a different anti-TNF agent. Close to 75% of the patients who were switched continued the second drug until the end of the study. If the

second drug was discontinued, this decision was usually made for the same reason as for the initial antiTNF agent.

Substitution, on the other hand, which is different from switching, implies interchangeability. If a biosimilar is said to be interchangeable or substitutable by the FDA, then it may be substituted for a reference drug by someone other than the prescribing rheumatologist (usually the pharmacist), without the agreement of either the patient or the rheumatologist. Drug substitutions can take place for several reasons:

- A health plan requires the use of a less expensive biosimilar rather than the reference drug, although the patient has responded well to the reference drug.
- A health plan changes the preferred biologic or biosimilar in their formulary resulting in a substitution by the dispensing pharmacist. Formularies can change (often based on price) multiple times a year, and multiple substitutions can occur within a short time interval.

Approval of a biosimilar does not mean that it meets the FDA standards for an interchangeable drug. For a biosimilar to meet the FDA standards to be labelled interchangeable with the reference drug, the biosimilar must:[26]

- Produce the same clinical result as the reference product in any given patient
- Have the same mechanism of action as the reference drug
- Have the same method of administration as the reference drug
- Have the same dosage and form as the reference drug
- If given to a patient more than once, the risk of safety and effectiveness must be the same as with the reference drug

According to Dörner and Kay,[27] multiple changes in biopharmaceuticals can result in "immunogenicity that could compromise the efficacy and safety" (Page 720) of all or some of the medications that a patient is taking. They recommend that frequent substitutions should be avoided, because even small differences in the products can "trigger an immune response" (Page 720) that is new to the patient.

Differences between many of the different biologics (reference drugs and biosimilars) are expected because of the complexity in manufacturing and storage of these medications. To minimize differences, manufacturers are required to have very detailed, tight quality controls on every step in the manufacture, storage, and distribution of these drugs.

In 2011, Schiestl et al.[28] published a Letter to the Editor of *Nature Biotechnology*, in which they described the results of a small study of changes in three biologics from 2007 to 2010. Two of the drugs evaluated are commonly used to treat rheumatic diseases—rituximab and etanercept. Although the report found

significant changes between different lots of all the brand name drugs tested, there did not appear to be any change in their "clinical profile[s]." These findings cannot be extrapolated to all biologics; therefore, these drugs need to be carefully monitored to ensure that clinically significant changes in reference drugs (and biosimilars) do not occur from lot to lot.

Different patients may respond differently to different biologics in the same class. For example, rheumatologists know that not all patients respond in the same way to all anti-TNF agents, although all these drugs have the same mechanism of action. In fact, although an individual may respond well to a biologic initially, they may develop resistance to that drug over time, and may or may not respond well to a different biologic in the same class.[29, 30] Another example is documented in a 2015 study by Reggia et al.[31] that compared the intravenous (IV) and subcutaneous (SQ) administration of abatacept. Of the 51 patients previously treated with IV abatacept, 14 (27%) relapsed after SQ administration and required a change back to the IV formulation of the drug. Fortunately, all patients responded well to the reinstitution of IV therapy.

In January 2017, the FDA provided guidance on the nonproprietary naming of biological products (Section 351a of the PHS Act (42 U.S.C. 262(a)(1)(B)(i)). Under this naming convention, the nonproprietary name designated for each originator biological product and each biosimilar product will be a proper name that combines a core name with a distinguishing suffix that has no meaning and is composed of four lower case letters.[32] However, in March 2019 the FDA updated this draft guidance; under the new guidance, approved biologics would no longer receive four-letter suffixes without meaning. Rather, the FDA would continue to assign suffixes to newly approved biologics and biosimilars. If a biosimilar was determined to be interchangeable it would receive its original nonproprietary name along with a suffix.[32] The FDA is still considering the appropriate suffix format for interchangeable products. This naming convention is intended to facilitate pharmacovigilance, accurate identification of these products by healthcare providers and patients and prevent the inadvertent substitution of products that have not yet been determined to be interchangeable.

In January 2017, the FDA issued a draft for public comment on the requirements for supporting labelling of biosimilar products as interchangeable with a reference product or brand-name biosimilar.[33] For a biosimilar to be considered for approval as an interchangeable drug, a manufacturer must demonstrate that the drug meets all of the requirements to be approved as a biosimilar and results in the same clinical outcomes as the reference drug in any patient and in all the referenced drug approved indications.

Switching studies will be required to determine whether or not alternating between the biosimilar and its reference product at least twice impacts the safety, efficacy, or immunogenicity of the treatment. Manufacturers will need to work closely with the FDA on study designs that can demonstrate interchangeability. The evidence required to demonstrate interchangeability will depend on the characteristics of the drugs and will vary for different biosimilars.

European Experience with Biosimilars

In 2005, the European Union (EU) established an approval pathway for biosimilars that had been available there since 2006. The European Medicines Agency (EMA) is responsible for the development of pathways for drug approval in the EU and approves drugs on a product-by-product basis. Usually, the pathways

indicate the patient populations to be included in both the clinical and nonclinical studies. The agency requires a biosimilar to demonstrate equivalent efficacy and safety to the reference drug in at least one randomized, double-blind study conducted over an adequate amount of time.[34] The EMA does permit extrapolation of safety and efficacy data from studies in a specific indication for use of a drug in other indications as long as those indications involve the same mechanism of action. However, if different cell receptors are involved in the mechanism of action for a different indication, the agency may require clinical studies involving a second patient population. The EMA also requires specific quality-control management plans that are both "proactive and product specific" to collect data on adverse events, just as it does for the reference drug.[34]

By the end of 2018, the tight regulatory requirements and complexity of biosimilar development resulted in EMA approval of 68 biosimilar drugs, including the biosimilar biologics used by rheumatologists as listed in Table 1. The remaining 45 drugs, which are not included in the table, are biosimilars for insulin, somatotropin, bevacizumab, trastuzumab, enoxaparin sodium, Interferon alfa-2a, epoetin alfa (Procrit® or Epogen®), and filgrastim (Neupogen®).[35] As of November 2019, 25 drugs that might be used by rheumatologists were approved in the EU. Some of the manufacturers of biosimilars are also manufacturers of reference drugs. The resources needed for the approval process and the costs of drug development and quality control has limited the number of companies entering the biosimilar market in the EU.

The EU experience has demonstrated that, compared with the reference product, biosimilars do not always have the dramatic effect on prices seen with small-molecule generic drugs. For example, in 2006 Omnitrope®, marketed by Sandoz, was approved by the EMA. The reference drug for Omnitrope is Genotropin®, or growth hormone. Omnitrope was priced 30% lower than the reference drug; however, 2 years later, it only had 2% of the market in Italy, Germany, France, and the United Kingdom (UK). In 2010, in an attempt to lower the cost of growth hormone, the UK decided that Omnitrope and Genotropin were considered to be interchangeable and required that the least expensive available drug (Omnitrope or Genotropin) should be used.[34]

Table 1. EMA-approved biosimilar DMARDs

Reference Drug	Biosimilar DMARD
Infliximab	• Flixabi® • Zessly • Inflectra® • Remsima®
Etanercept	• Benepali® • Erelzi® ● Nepexto

Adalimumab	• Amgevita® • Amspar • Cyltezo® • Halimatoz® • Hefiya®	• Hulio® • Imraldi® • Kromeya	• Solymbic • Hyrimoz • Idacio
Rituximab	• Blitzima® • Ritemvia® • Rituzena®	• Rixathon® • Riximyo® • Truxima®	• Ruxience
Teriparatide	• Movymia® • Terrosa®		

DMARD(s), disease-modifying antirheumatic drug(s); EMA, European Medicines Agency

Interestingly, with the introduction of biosimilars, reference-drug prices have also decreased. In fact, in 2015, with the introduction of a biosimilar for the reference drug Remicade® in the UK, the manufacturer reduced the price for Remicade by 25% for the UK's National Health Service.[36]

By 2013, nearly 25% of all biologic sales in the EU were biosimilars, with no significant or unexpected adverse events reported.[37]

Biosimilar prices vary widely from country to country in the EU, with discounts averaging 15% to 40% when compared with the reference drugs. At the same time, prices for some of the reference drugs are falling to compete with the biosimilars. Haustein et al.[38] published a paper in which they developed models to predict potential cost savings in Europe between 2007 and 2020 through the use of biosimilars. The models included France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK. Based on their calculations, the use of biosimilars has the potential to result in overall cost savings between 11.8 and 33.4 billion Euros, with the greatest savings expected in France, Germany, and the UK. Biosimilar mAbs are expected to produce the greatest savings ranging from 1.8 to 20.4 billion Euros. Furthermore, savings for biosimilars of etanercept, rituximab, and trastuzumab alone could potentially amount to as much as 11.3 billion Euros, nearly 15% of the total spend for these reference drugs. Interestingly, savings were greater when a biosimilar was introduced immediately after a reference drug patent expired rather than several years after patent expiration. The authors also observed a decline in the price of the reference drug after the introduction of the biosimilar, resulting in an overall decrease in drug costs to the healthcare system but of little benefit to biosimilar manufacturers.
In addition, Haustein et al.[38] reported that physicians may be reluctant to substitute a biosimilar for the reference drug, because it is similar but not identical to the reference drug. The authors suggested that additional studies comparing the biosimilars to the reference drugs were needed, together with more education of the physician community.

Biosimilars in the United States

It is still unclear how biosimilars will be marketed and priced in the US and how payers will adjust their formularies when these drugs become more available. A very recent paper by Morton et al.[39] suggests two possibilities (Pages 3–4):

- The 10-year experience with biosimilars in Europe has resolved the discomfort that many providers have had with biosimilars with respect to efficacy and safety and therefore the use of biosimilars in the US will "be shaped by economic and institutional factors rather than as a result of meaningful differences in health care outcomes.

  OR

- The entry of biosimilars into the US healthcare system will have little impact on drug costs because, in the US market, very few biosimilars will be available as a result of the high cost of approval and price competition from the makers of the reference drugs, something which has already been seen in the European market.

In March 2015, the first biosimilar (Zarxio®) was approved in the US. Zarxio is manufactured by Sandoz and is a biosimilar for Neupogen (filgrastim). The drug was approved for the same indications as Neupogen. This approval comes 5 years after the BPCIA of 2009 was signed into law. (Zarxio was not approved as an interchangeable drug).[40]

As of November 2019, the FDA has approved 25 biosimilars, 13 of which may be used by rheumatologists; however, as of May 2019, none of these drugs have been labelled interchangeable. **Table 2** lists the biosimilars used by rheumatologists that are FDA approved for the indications listed.

Table 2. FDA-approved biosimilar DMARDs

Biosimilar DMARDs (bsDMARDs)	Originator Drug	Route of Administration	Indications
Erelzi® (etanercept-szzs)	Enbrel®	SQ	RA, PsA, AS
Eticovo (etanercept-ykro)	Enbrel®	SQ	RA, PsA, AS
Ruxience (rituximab-pvvr)	Rituxan	IV	Granulomatosis with polyangiitis and microscopic polyangiitis with steroids
Truxima (rituximab-abbs)	Rituxan	IV	RA in combination with MTX in patients who have failed to get an adequate response to at least one TNFi drug Granulomatosis with polyangiitis and - microscopic polyangiitis

Riabni (rituximab-arrx)	Rituxan	IV	Granulomatosis with polyangiitis with glucocorticoids and microscopic polyangiitis
Inflectra® (infliximab-dyyb)	Remicade®	IV	RA, PsA, AS
Renflexis® (infliximab-abda)	Remicade®	IV	RA, PsA, AS
Ixifi® (infliximab-qbtx)	Remicade®	IV	RA (when given with MTX), PsA, AS
Avsola (infliximab-axxq)	Remicade	IV	RA with MTX, PsA, AS
Amjevita® (adalimumab-atto)	Humira®	SQ	RA, PsA, AS
Cyltezo® (adalimumab-adbm)	Humira®	SQ	RA, PsA, AS
Hyrimoz® (adalimumab-adaz)	Humira®	SQ	RA, PsA, AS
Abrilada (adalimumab-afzb)	Humira®	SQ	RA, PsA, AS
Hadlima (adalimumab-bwwd)	Humira®	SQ	RA, PsA, AS
Hulio (adalimumab-fkjp)	Humira®	SQ	RA, PsA, AS
Hyrimoz (adalimumab-adaz)	Humira®	SQ	RA, PsA, AS

AS, ankylosing spondylitis; bsDMARDs, biosimilar disease-modifying antirheumatic drugs; DMARDs, disease-modifying antirheumatic drugs; FDA, Food and Drug Administration; IV, intravenous; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SQ, subcutaneous

A 2007 paper discussed potential savings from the entry of biosimilars into the US market.[41] The authors stated that the major reason generic drugs had such a dramatic effect on prices was the great number of choices for the same brand-name drug. More choices resulted in aggressive competition between manufacturers for market share, which in turn, lowered prices. The authors suggested there would not be as many entries in the biosimilar market as in the generic market as a result of high drug development costs, challenges obtaining FDA approval (which requires more clinical testing than is required for generics), and maintaining tight quality control of the production environment. For these reasons and several others described in the paper, this group together with others mentioned above, did not predict the same dramatic decrease in costs with the approval of biosimilars as those seen with generic small-molecule drugs. In addition, manufacturers of the reference drugs may, and already have, entered the biosimilars market. All these factors led the authors of this paper to predict that, in the US, the prices for biosimilars would not be much lower than those for the reference drugs.[41]

The choice of medication to treat rheumatologic diseases is complex and takes into account not only a patient's rheumatologic disease but also age, comorbid conditions, concurrent use of medications, the ability of the patient to self-administer drugs, patient compliance with drug schedules, and antibody status.

United Rheumatology strongly supports the following:

- Mandatory switching or substitution (interchangeability) of biopharmaceuticals, including biosimilars, **should not occur** without the consent of the prescribing rheumatologist and the agreement of the patient.
- Patients who have been treated with biologics and have reached either remission or low disease activity should not be required to change their medication(s) because of changes in health plan formularies or cost. Forcing patients with stable disease to change medications may put them at risk of flares and increased disease activity.[31]
- Substitution should only occur when the FDA has designated a biologic product as interchangeable and only with the approval of the prescribing rheumatologist.
- Additional clinical studies that demonstrate the safety and efficacy of extrapolation of indications for the use of biosimilars.

United Rheumatology's position on these issues is consistent with that of the ACR.[13]

For patients who have not received any biologic treatment (bio-naïve patients) for a rheumatologic disease, United Rheumatology supports the use of an appropriate biosimilar, if one is available. Biosimilars will hopefully lower the cost of these life-altering drugs, making them available to more patients who need them. Unfortunately, IMS Health data for Zarxio has not demonstrated an increase in utilization as a result of the introduction of a biosimilar into the filgrastim space. Biosimilars should certainly lower the cost to the payer and thereby save money in the healthcare economy, but they may not lower the cost to the patient, whose copayments may remain the same. Even if the copayment is greater for the higher "tiered" product, it is likely that the manufacturer of the originator will offer copayment assistance to offset the difference. This is a practice frequently seen when a drug (e.g., Celebrex®) "goes" generic.

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Document Updates

Document Version	Description of Changes	Approval Date
1.1.2017	Creation of first version	Mar 2017
1.1.2019	2018/19 Update	Mar 2019
1.1.2020	Addition of new drugs; update references	
1.1.2021	Addition of new drugs	April, 2021
1.1.2023		Feb 2023