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# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACA</td>
<td>Patient Protection and Affordable Care Act</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AS</td>
<td>Ankylosing spondylitis</td>
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<tr>
<td>BPCIA</td>
<td>Biologics Price Competition and Innovation Act</td>
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<tr>
<td>DNA</td>
<td>Deoxynucleic acid</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>PsA</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>SpA</td>
<td>Spondyloarthritis</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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</table>
Introduction

The introduction of biologic medications over the last 3 decades has been life-changing for many patients suffering with a wide variety of diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), ulcerative colitis (UC), 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 be very effective in slowing 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.” There is no standard definition of a specialty drug; however, often medications are considered specialty drugs when the annual cost of treatment is above a predefined threshold amount. For example, Medicare considers a medication to be a specialty drug when the annual cost is $600 or more. In some cases, the cost of a specialty drug can exceed $100,000 per year. Other parameters used to place a medication into the specialty-drug group include but are not limited to the following:

- Treats an unusual or rare condition
- Needs special handling (i.e. refrigeration during shipping and storage)
- Has a limited distribution network
- Requires tight quality control and ongoing re-evaluation of efficacy, safety, and adverse immune response

Because these medications are priced so high, health plans often impose cost sharing rules, making some of the treatments unaffordable to patients, even to patients with insurance.

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, there were only ten specialty drugs available in the United States (US) in 1990; by 2012, there were close to 300. It is estimated that close to half of the drugs in the current drug pipeline will fall into the specialty-drug category. In 2014, specialty drugs accounted for only 1% of the prescriptions written in the US, but for 31.8% of all drug spending. According to the Institute for Human Data Science (IQVIA™), drug spending in the US reached $450 billion in 2016, based on invoice prices. After adjusting for estimated rebates and other price concessions by manufacturers, net spending was $323 billion, up 4.8% from 2015. According to the IQVIA report, the average cost of pharmaceuticals per capita in the US was approximately $895, of which $384 was spent on specialty drugs. Specialty drugs accounted for 39.6% of all drug spend, based on invoice pricing, and for 42.9% of all drug spend after rebates and other price concessions.

Most drugs used in the US are not biologics. These traditional drugs (also known as small molecules or chemical drugs) have a specific chemical formula that can be reproduced by “combining specific chemical ingredients in an ordered process.” 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.” In addition, generics are less costly than brand-name drugs. The Congressional Budget Office estimates that generics save patients $8 to $10 billion annually.

According to the American College of Rheumatology (ACR), the most common biologics used to treat rheumatologic disorders are monoclonal antibodies. They can be 200 to 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 which are “therapeutic proteins” or “monoclonal antibodies.”

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

Although manufacturers of biosimilars have access to the brand-name manufacturer’s biologic agents, unlike generic drugs, manufacturers of biosimilars do not have access to the brand-name manufacturer’s process; they must therefore “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, has summarized the manufacturing process as follows (Page 2):

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 post-translational 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 ACR statement above, 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.”

United Rheumatology Clinical Practice Guideline
Biosimilars V1.1.2018
Recommendations for the Use of Biosimilars in the Management of Rheumatologic Disorders

In 2017, a multidisciplinary and multinational Task Force published consensus recommendations for the use of biosimilars in the management of rheumatological diseases. Members of the Task Force included different specialists—17 rheumatologists, a dermatologist, a gastroenterologist, two pharmacologists, as well as two patients with rheumatic diseases, and a research fellow. The members came from eight European countries, Japan, and the US. The Task Force performed a systematic review of the literature, including abstracts presented at both the 2015 and 2016 meetings of the ACR and European League Against Rheumatism (EULAR). The Task Force developed five overarching principles and eight consensus recommendations.

The overarching or comprehensive principles included the following:

- Management of rheumatologic disorders should take into consideration a “shared decision-making process between patients and their rheumatologists” (Page 3). This principle is not just for biosimilars or biologics but applies to all treatment decisions in rheumatology.
- “The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made” (Page 3). This is especially true in the US, where patients are covered by a wide variety of different insurers with different coverage policies. The cost and availability of some medications and treatments must be part of the shared decision-making process to ensure that treatment is accessible and affordable for patients.
- When a biosimilar has been approved for use by regulatory agencies, it is considered to be neither better nor worse than the reference drug and as safe as the reference drug.
- Patients and healthcare providers should be educated about biosimilars including the robust FDA approval process, and “their safety and efficacy” (Page 4).
- “Harmonized methods should be established to obtain reliable pharmacovigilance data, including traceability, about biosimilars and bio-originators [reference drugs]” (Page 4).

The following recommendations of the Task Force were agreed to by consensus:

- Biosimilars must lower the cost of treatment and improve access to the best treatment for all patients with rheumatic disorders.
  The savings payers realize from the lower-cost medications must be transferred back to patients by improving access, or lowering either pharmaceutical copays or co-insurance, or by lowering premiums. The European experience with biosimilars has shown price differences of 20% to 40% below the original reference drugs. Generic drugs, on the other hand, have reduced drug prices by 80%.
- Biosimilars can be used in the same way as the reference drug is used.
  After approval by regulatory agencies biosimilars “can be considered to be essentially the same biologic as a new batch of the [reference drugs]” (Page 5).
• Healthcare providers do not need to test for antidrug antibodies to biosimilars because up to the present time no “significant differences” (Page 5) between biosimilars and their reference drugs have been found.

• “Relevant preclinical and Phase I data on a biosimilar should be available when Phase III data are published” (Page 6).

• Demonstration of effectiveness and safety for one indication is adequate to allow for extrapolation to other diseases for which the reference drug is approved for use.

• A one-time switch from a reference drug to one of its biosimilars is safe, based on the currently available literature. Patient preference should be considered.

• Switching multiple times between biosimilars and their reference drugs requires further study.

• Switching between reference drugs and biosimilars or between biosimilars should not occur without the knowledge of the patient and healthcare provider.

The development of guidelines for the clinical use of biosimilars is still in its infancy. Over the next few years, as increased numbers of biosimilars enter the market place, United Rheumatology anticipates that more and expanded evidenced-based guidance will become available. The literature will be continually reviewed and updated, as appropriate.

**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,\(^ {13}\) retail prescriptions for generics made up 74.5% of the small-molecule retail prescriptions in the US in 2009. In 2014, prescriptions for generic drugs accounted for 88% of the prescriptions in the US.\(^ {14}\)

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.\(^ {13}\) Manufacturers of generic drugs are now required only to demonstrate that their product can be safely substituted for the brand-name drug and is bioequivalent to the brand-name 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. Food and Drug Administration 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.\(^ {15,16}\)

Biosimilars (sometimes referred to as follow-on-biologics), however, are not exact copies of the reference (brand-name or bio-originator) drug but are similar to it. Recently, interest in biosimilars has been increasing as brand-name reference drug patents expire. It is hoped that biosimilars will result in a reduced overall spend on biologics, similar to the effect that generics had on small-molecule drugs.
Several years ago, Congress became concerned with the rapidly rising costs of biologic medications. In an effort to encourage the availability of more cost-effective treatments, Congress 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. The process allows for minor differences in inactive ingredients in biosimilar drugs when compared to the brand-name biologic or reference drug. The law also contains a section that allows for the possibility that biosimilars might be interchangeable with the brand-name reference drug. Accordingly, 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 healthcare provider who prescribed the reference product.17

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 for interchangeability with the reference drug, the interchangeable biological product must meet the standards for a biosimilar and the following:18

- The interchangeable product is expected to produce the same clinical result as the reference product in any given patient
- If given to a patient more than once, switching between the interchangeable product and the reference product must not increase safety risks nor decrease effectiveness compared to using the reference product without switching between the two products.

At first glance, the provisions of this section of the ACA appear to be similar to the 1984 legislation for the expedited approval of generics (Waxman-Hatch Act), but there are some differences. Approval of biosimilars requires preclinical and clinical data that is more extensive than just the demonstration of structural equivalence and bioequivalence as is required for generic approval. 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).19 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, quality requirements for biosimilars, and include questions and answers concerning the implementation of the 2009 BPCIA.20 This document also provided 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.

Although the cost of developing and obtaining approval for biosimilar drugs is significantly greater than that for generics, it is significantly lower than for the reference agents. Accordingly, discounts in pricing of 15% to 30% from the average wholesale price of the reference product biosimilars are expected.
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 SpA can be a painstaking task often marked by trial and error. Not every patient with the same disease and disease activity responds to the same biologic. There are even differences in the response of different patients to different biologics in the same class. Once a patient is in remission or as close to it as possible, it is important to maintain that clinical response level and to avoid and/or delay the onset of flares. Rheumatologists might be reluctant to change medications in stable patients, 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 to the reference drug.9

### 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 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 was safe without any decrease in efficacy, then rheumatologists might consider whether or not a change or switch was appropriate for their patients. Both the provider and the patient must be comfortable with the switch.

A provider may recommend switching medications for several different reasons, which may include:

- Decreasing patient out-of-pocket cost
- Drug toxicity
- Change in payer formulary
- Failure to respond
- Development of anti-drug antibodies

A 2007 publication in *Arthritis and Rheumatism*21 describes the experience of 6739 patients with RA treated with anti-tumor necrosis factor (TNF) medications. Over approximately 15 months, 841 patients stopped the first drug because it was ineffective, and another 1023 patients stopped the first drug 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 on the second drug until the end of the study. When the second drug was discontinued, the decision was usually made for the same reason as for the initial anti-TNF agent.21

Substitution, on the other hand, is very different from switching. Substitution 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 provider (usually the pharmacist), without the agreement of either the patient or the rheumatologist. However, different states have different rules and regulations regarding pharmacist drug substitutions. According to the Coalition of State Rheumatology Organizations, some states have already adopted or are working on legislation that would prevent biosimilar drug substitution for nonmedical reasons such as the two listed below.22
Biosimilar substitutions could occur 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 could potentially occur within a short time interval.

When and if a drug is approved as interchangeable, the FDA states that:

Prescribers and patients can expect that the interchangeable product will have the same clinical result as the reference product. Prescribers and their patients can be assured that an FDA-approved interchangeable product has been thoroughly tested and has met the FDA’s high standards for approval. Meeting these standards means that healthcare professionals and patients can be assured of the safety and effectiveness of an interchangeable product, just as they would be for a reference product.

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

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

In 2011, Schiestl et al. published a Letter to the Editor of Nature Biotechnology, in which they describe the results of a small study looking at changes in three biologics from 2007 to 2010. Two of the drugs evaluated—rituximab and etanercept—are commonly used to treat rheumatic diseases. The report found that there were significant changes between different lots of the drugs tested. However, there did not appear to be any change in their “clinical profile[s].” Although the findings in this small study cannot be extrapolated to all biologics, these drugs need to be carefully monitored to ensure that clinically significant changes do not occur from lot to lot of reference drugs (and biosimilars).

Different patients may respond differently to different biologics in the same class. For example, rheumatologists know that not all patients respond the same way to all anti-TNF drugs, despite the fact that they all have the same mechanism of action. In fact, an individual may respond well to a biologic initially and then, over time, develop resistance to that drug but may or may not respond well to a different biologic in the same class.

Another example of how differences in the same drug may result in different patient responses is documented in a 2015 study by Reggia et al. comparing the abatacept (Orencia®) intravenous administration to subcutaneous administration. They reported that, of 51 patients previously treated with intravenous abatacept, 14 (27%) of the patients relapsed when changed to subcutaneous administration.
and required a change back to the intravenous form of the drug. Fortunately, they all responded well to the re-institution of intravenous therapy.

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. Public comments were due by May 9, 2017. The final guidance document on interchangeable biosimilars has not yet been published. Currently, no biosimilar drugs have been designated as interchangeable.

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 result as the reference drug in any patient and in all of the approved indications of the referenced drug.

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 vary for different biosimilars, depending on the characteristics of the drugs.

**FDA Recommendations for Naming of Biologics**

In January 2017, the FDA published final guidance for the naming of both biosimilars and their reference drugs. According to this publication, naming of biological products should meet a national naming convention for every biological product (reference drugs, biosimilar product) and should have a proper name that is “a combination of the core name and a distinguishing suffix [FDA approved] that is devoid of meaning and composed of four lowercase letters” (Page 1). (for current biosimilars names, see Table 1, *Biosimilars in the United States*). The FDA suggests that this naming convention should apply to reference drugs and biosimilars that have already been approved.

For reference drugs, the core name will be the name adopted by the US Adopted Names Council. For biosimilars, per FDA guidance, the core name should be the same as the core name of the previously licensed product with a suffix (attached with a hyphen) of four lowercase letters that have no meaning.

This naming convention is intended to facilitate pharmacovigilance and 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.

**European Experience with Biosimilars**

In 2005, the European Union (EU) established an approval pathway for biosimilars, which have been available in that region since 2006. The European Medicines Agency (EMA), which is responsible for the development of pathways for drug approval in the EU, uses them to approve 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 studies demonstrating that a biosimilar is comparable in...
efficacy and safety to the reference drug in at least one randomized, double-blind study conducted over an adequate period of time to demonstrate equivalent efficacy. The EMA permits extrapolation of the safety and efficacy data from the studies of a specific indication to other indications for use of a drug 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, then 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.

The tight regulatory requirements and the complexity of development of biosimilars has resulted in EMA approval of only 26 biosimilar drugs by the end of 2017, including:

- Flixabi, Remsima, and Inflectra (reference drug, infliximab)
- Benedali and Erelzi (reference drug, etanercept)
- Imraldi, Cyltezo, Solymbic, and Amgevita (reference drug, adalimumab)
- Blitzima, Rituzena, Rixathon, Riximyo. Truxima, and Ritemvia (reference drug rituximab)
- Terrosa and Movymia (reference drug, teriparatide)

The remainder are biosimilars for insulin, epoetin alfa (Procrit® or Epogen®), and filgrastim (Neupogen®). 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 have limited the number of companies entering the biosimilars market in the EU.

The EU experience has demonstrated that biosimilars do not always have the dramatic effect on prices that has been 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) be used.

By 2013, according to Quintiles IMS, nearly 25% of all biologic sales in Europe were biosimilars, with no significant or unexpected adverse events reported.

Biosimilars prices vary widely from country to country in Europe, with discounts averaging 15% to 40% when compared to the reference drugs. At the same time, prices for some of the reference drugs are already falling to compete with the biosimilars. Haustein et al. 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 authors expected to see the greatest savings (1.8 billion to 20.4 billion Euros) in France, Germany, and the UK with biosimilar monoclonal antibodies. Savings for biosimilar
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 when compared to the introduction of a biosimilar 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 in little benefit to biosimilar manufacturers.

Haustein et al.\textsuperscript{35} also reported that physicians may be reluctant to substitute a biosimilar for the reference drug, because the biosimilar is just similar but not identical to the reference drug. The authors suggest 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**

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 2009 BPCIA was signed into law. (Zarxio was not approved as an interchangeable drug). Teva received approval for its Granix (tbo-filgrastim) in 2012, at which time the FDA did not have a formal pathway for approval of biosimilars; as a result, it was only approved for one indication, the management of neutropenia in patients with a non-myeloid malignancy being treated with myelosuppressive chemotherapy.\textsuperscript{36} Since 2015, eight other biosimilar drugs have been approved in the US with more in the pipeline. Table 1 lists the approved biosimilars and their indications as of the writing of this guideline.
### Table 1. Biosimilar drugs approved by the FDA

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<th>Reference drug brand name</th>
<th>Name according to FDA recommendations</th>
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<td>Neupogen® tbo-filgrastim</td>
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*When this drug was approved by the FDA there was no formal process in place for approval of biosimilar drugs and the indications for the use of Granix are limited. Technically, it is not considered to be a biosimilar.

AS, ankylosing spondylitis; FDA, Food and Drug Administration; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis

It is still unclear how biosimilars will be marketed and priced in the US. It is also unclear how payers will adjust their formularies when these drugs become more available. A very recent paper by Morton et al. suggests two possibilities:

- 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. 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 healthcare outcomes” (Pages 3-4).

  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

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approval and price competition from the makers of the reference drugs, as has already been seen in the European market.

A 2007 paper discussed potential savings from the entry of biosimilars into the US market. The authors stated that the main reason that generic drugs had such a dramatic effect on prices was the great number of the same brand drug, which resulted in aggressive competition between manufacturers for market share and, in turn, lowered prices. The authors suggested that there would not be as many entries in the biosimilar as in the generic market due to the high costs of drug development, more clinical testing than that required for generics to obtain FDA approval, and the maintenance of tight quality control of the production environment. For these reasons and several others described in the paper, this group (as others mentioned above) does not predict the same dramatic decrease in costs with the approval of biosimilars as the one seen with generic small-molecule drugs. In addition, manufacturers of the reference drugs themselves may enter, and already have entered, the biosimilar market. Thus, in the US, the prices for biosimilars may be not much lower than those of the reference drugs.

Since the publication of this paper, the FDA has approved several biosimilar drugs in the US. There has also been more intense education of physicians relating to these drugs and the FDA-approval process for them. It is hoped that these two factors will increase the use and decrease the cost of biosimilars.

In 2014, the Rand Corporation published a Perspective on the potential cost savings to the US healthcare system with the more widespread use of biosimilars. According to this publication, an estimated potential cost savings of $44.2 billion by 2024, as a result of the increased adoption of biosimilars, can be projected for the US.

It may be reasonable to expect significant decreases in the cost of biosimilars compared to brand-name reference drugs only when there are multiple biosimilars available for the same product. This is just starting to occur in the US, with an estimated 43 biosimilars currently in clinical development. As more of these drugs enter the market, we may see more substantial savings to the healthcare system in general and better access to biologic treatments by more patients.

However, price differentials between reference drugs and biosimilars so far have not been as large as was expected (approximately 15% below the reference drug). In July 2017, Merck announced that it would market its biosimilar Renflexis (reference drug Remicade®) 35% below the cost of the reference brand-name drug.

The choice of medication to treat rheumatologic diseases is a complex one, which 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:

- 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 stable patients to change medications may put these patients at risk for flares and increased disease activity.\textsuperscript{28}

• Substitution should only occur when the FDA has designated a biologic product as interchangeable, and only with the approval of the prescribing physician and patient.

• Additional clinical studies are needed to demonstrate the safety and efficacy of using extrapolation of indications in the use of biosimilars.

United Rheumatology’s position on these issues is consistent with that of the ACR.\textsuperscript{9}

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 and less expensive than the reference drug. Biosimilars will hopefully lower the cost of these life-altering drugs, making them available to more patients who need them.
References


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## Document Updates

<table>
<thead>
<tr>
<th>Document Version</th>
<th>Description of Changes</th>
<th>Approval Date</th>
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<tr>
<td>1.1.2017</td>
<td>Creation of first version</td>
<td>03 Mar 2017</td>
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<tr>
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<td>2018 literature update</td>
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