





SPECIAL ARTICLE

# The Science Behind Biosimilars

## Entering a New Era of Biologic Therapy

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### Introduction

An important challenge currently facing rheumatologists and rheumatology health professionals is to gain an understanding of the landscape surrounding biosimilar agents, including the scientific, clinical, economic, and prescribing issues related to their use. The US Food and Drug Administration (FDA) defines a biosimilar as a biologic product that is “highly similar to” an approved biologic product (the “reference,” “originator,” or “bio-originator” product) and that has “no clinically meaningful differences” in safety or effectiveness as compared to the reference product (1). The number of biosimilars in development has burgeoned since the Biologics Price Competition and Innovation (BPCI) Act of 2009 was passed by the US Congress with the intent of reducing

costs and thereby increasing patients’ access to biologics. Another factor driving development of biosimilars is that the exclusivity period, as defined by the FDA, is approaching completion for several biologics.

Nomenclature for biosimilars in the US uses the common nonproprietary name followed by a 4-letter suffix, so that each drug, both reference product and biosimilar, will have a unique nonproprietary name. Proprietary names, in contrast, are generated by the manufacturer and may vary from country to country for the same drug. As of December 2017, the FDA had approved 9 biosimilars, 6 of which are tumor necrosis factor (TNF) inhibitors, for rheumatologic and other inflammatory diseases: infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), and infliximab-qbtx (Ixifi) (biosimilars of infliximab [Remicade]), etanercept-szsz (Erelzi) (biosimilar of etanercept [Enbrel]), and adalimumab-adbm (Cyltezo) and adalimumab-atto (Amjevita) (biosimilars of adalimumab [Humira]) (2–5). Many additional biosimilars of reference products with indications for both rheumatologic and nonrheumatologic diseases are under development. An updated list of approved biologics and biosimilars is available online in the “Purple Book” through the FDA Center for Drug Evaluation and Research (6).

Biosimilars should not be confused with generic medications, despite the fact that for both, pathways for regulatory approval are abbreviated as compared to the pathways for approval of new drugs (Figure 1). The chemical structure of a generic small-molecule drug must be identical to that of its reference product. Thus, once chemical identity has been demonstrated, approval of a generic drug may rely upon a study demonstrating pharmacokinetic equivalence to the reference drug. Subsequent comparative clinical trials to demonstrate efficacy equivalent to that of the reference drug are not required.

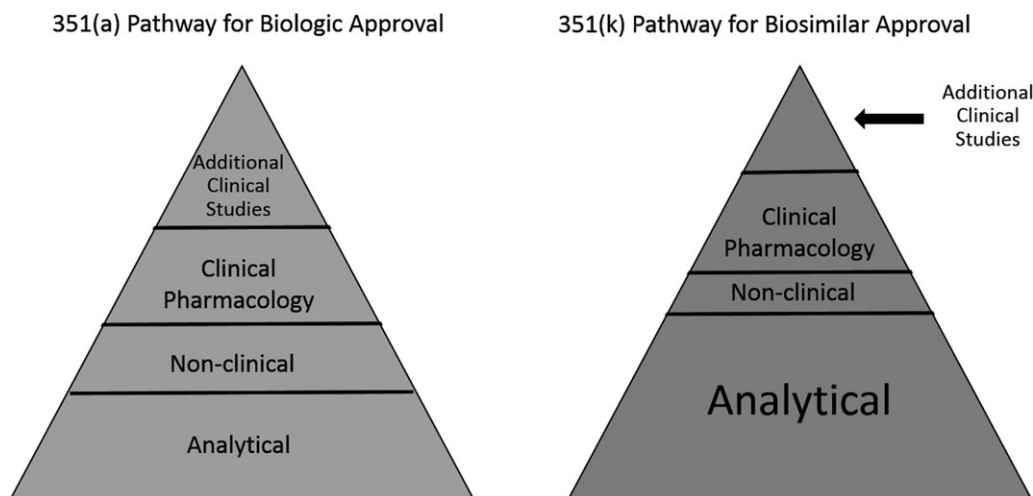
In contrast, because biologics are proteins produced in living cells, biosimilars usually are not identical

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**Figure 1.** US Food and Drug Administration (FDA) pathways for approval of biologic drugs and biosimilar drugs. The FDA uses a “totality of the evidence” approach to demonstrate biosimilarity. Adapted from <https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm378510.pdf>.

to their reference products. The biosimilar manufacturer reverse-engineers the DNA sequence based on the primary protein sequence of the reference drug (available in the public domain). The synthesized gene is then transfected into host cells, in which transcription and translation mechanisms generate the core protein of the biosimilar. Several factors integral to the manufacturing process influence the degree to which the molecular structure of the biosimilar matches that of its reference product. These include choice of host cell, which influences posttranslational modifications of the protein (e.g., glycosylation [7]), and methods used to purify and stabilize the final product. Importantly, to achieve FDA approval, a biosimilar must be highly similar in structure and function, equivalent in efficacy, and comparable in safety and immunogenicity to its reference product, despite potential slight molecular differences between the 2 agents.

### Regulatory pathways for approval

The BPCI Act established an abbreviated pathway for FDA approval of biosimilars. Subsequently, the FDA has issued guidance documents (8,9) that detail the requirements for demonstrating biosimilarity (Figure 1). Similar guidance has been issued by the European Medicines Agency (EMA), an analogous regulatory body in Europe (10).

The FDA has adopted a “totality of the evidence” approach to the approval of biosimilars, in which multiple lines of evidence are integrated to determine biosimilarity by the reduction of “residual uncertainty.” The regulatory pathway for biosimilar development (351[k]) mandates a

sequential series of rigorous comparative studies to demonstrate biosimilarity of the biosimilar candidate to its reference product (8–10). It places heavy emphasis on pre-clinical analytical comparison of structure and function between the proposed biosimilar and its reference product (Figure 2), as well as comparative clinical studies of pharmacokinetic parameters and, if a relevant biomarker is available, of pharmacodynamic parameters. The FDA also requires assessment of the stability and formulation of the biosimilar. In addition, at least one clinical trial comparing the proposed biosimilar to its reference product, in patients with a disease for which the reference product is indicated, is required in order to assess equivalence of efficacy and comparability of safety and immunogenicity. Once a biosimilar has satisfied the requirements of this regulatory pathway, both patients and providers should expect that clinical outcomes with the biosimilar will parallel the accumulated experience with the use of its reference product.

### Immunogenicity and scientific aspects of manufacturing

**Drift and evolution.** Batches of originator biologics administered to patients today often differ from those of the same drugs that were dispensed in previous years, particularly for drugs introduced in the late 1990s and early 2000s (11). Such differences are due to both drift and evolution—the intentional and unintentional alterations in manufacturing that result in lot-to-lot variability of both monoclonal antibodies and fusion proteins (12). The manufacturers of virtually every originator biologic have made intentional, post-approval changes to their manufacturing processes, each of which

**General**

- pH/osmolality
- Extractable volume
- Protein concentration
- Subvisible particle
- Visible particle
- Appearance

**Structural Characterization**

- Molecular weight by mass spectrometry
- Amino acid sequencing by LC-MS
- Peptide mapping by trypsin, Lys-C, and Asp-N protease digestions
- Disulfide bond analysis
- Free sulfhydryl group quantification
- N-terminal sequence analysis
- C-terminal sequence analysis
- Methionine oxidation by LC-MS
- Deamidation by LC-MS

**Higher-Order Structural Characterization**

- HDX/MS
- Ultraviolet spectroscopy
- Differential scanning calorimetry
- Micro-flow imaging
- Dynamic light scattering
- SC-MALLS analysis
- Fluorescence spectroscopy: intrinsic, extrinsic
- Fourier-transformed infrared spectroscopy
- Circular dichroism: near and far
- SV-AUC
- Extinction coefficient

**Glycan Profile**

- N-linked glycosylation site
- N-glycan identification by LC-MS
- N-glycan profile by 2-amino benzamide (2-AB) ultra-performance liquid chromatography
- Fc-specific glycan profile
- O-glycan site by LC-MS
- O-glycan profile by  $\beta$ -elimination
- Total sialic acid

**Purity/Impurity**

- HPLC
- Size-exclusion HPLC
- Cation-exchange HPLC
- Protein A/protein G HPLC
- CE-SES, reduced and nonreduced
- Imaged capillary isoelectric focusing

**Mechanism of Action–Related Biologic Assays**

- TNF binding assays: FRET; SPR
- LTA binding assay: FRET, SPR
- Neutralization assay: Cell

**Non–Mechanism of Action–Related Biologic Assays**

- Fc $\gamma$ R binding assays: AlphaScreen, SPR
- FcRn binding assays: AlphaScreen, SPR
- C1q binding assays: ELISA, SPR
- Complement-dependent cytotoxicity assay
- Apoptosis assay

**Figure 2.** Characterization methods, classified according to quality attributes, used to evaluate the structural, physicochemical, and biologic characteristics of SB4, a biosimilar of etanercept. LC-MS = liquid chromatography mass spectrometry; HDX/MS = hydrogen/deuterium exchange/mass spectrometry; SC-MALLS = size exclusion chromatography–multiangle light scattering analysis; SV-AUC = sedimentation velocity–analytical ultracentrifugation; HPLC = high-performance liquid chromatography; CE-SES = capillary electrophoresis–sodium dodecyl sulfate; TNF = tumor necrosis factor; FRET = fluorescence resonance energy transfer; SPR = surface plasmon resonance; LTA = lymphotoxin  $\alpha$ ; Fc $\gamma$ R = Fc $\gamma$  receptor; AlphaScreen = amplified luminescent proximity homogeneous assay; FcRn = neonatal Fc receptor; ELISA = enzyme-linked immunosorbent assay. Adapted from Cho IH, Lee N, Song D, Jung SY, Bou-Assaf G, Sosic Z et al. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. *MAbs* 2016;8:1136–55.

is reviewed and approved by regulatory agencies (13,14). Regulatory agencies permit such changes if they fall within predetermined proven acceptable ranges when the products are carefully monitored using sophisticated analytical techniques. Thus, for originator biologics, the effects of drift and evolution accrue over time after their approval. This will continue to occur, not only for reference drugs, but also for approved biosimilars. Despite the occurrence of drift and evolution in the manufacture of virtually all commercially available biologic medications, these originator biologics have continued to be safe and effective. Accordingly, favorable outcomes in comparative analytical, clinical, and immunologic studies, with rigorous regulatory oversight and careful post-marketing pharmacovigilance, should reassure patients and prescribers that biosimilars will be both as safe and as effective as their reference products.

**Immunogenicity.** Another critical component of the biosimilar approval pathway strives to ensure comparable immunogenicity of biosimilars and their reference products.

This includes measurement of both binding and neutralizing antidrug antibodies, which have been well characterized in patients treated with originator biologics for rheumatologic conditions (15,16). Antidrug antibodies have been detected in patients taking originator biologics, such as infliximab or adalimumab, and are associated with lower trough drug concentrations, reduced efficacy, and increased frequency of infusion reactions (17,18). The prevalence of antidrug antibodies varies widely among studies, depending on the assay used for their detection (16).

Protein aggregation or impurities introduced during the manufacturing process of any biologic agent may stimulate antidrug antibody formation. Although the primary structures of biosimilars must be identical to those of their reference products, there may be differences in secondary (e.g.,  $\alpha$ -helix and  $\beta$ -sheet), tertiary (e.g., disulfide and salt bridges), or quaternary (e.g., protein subunit interactions) structure as well as differences in glycosylation and other posttranslational modifications. Theoretically, these structural differences may also induce the

development of antidrug antibodies in patients initially exposed to the reference product (7). Thus, both the FDA and EMA mandate at least 1 clinical trial in which comparative immunogenicity of a biosimilar and its reference product is assessed (8,10).

For some biosimilars, regulatory agencies may require a clinical trial that includes a single crossover from the reference product to the proposed biosimilar, to assess whether this transition induces antidrug antibody formation with a resultant loss of efficacy. If a biosimilar is intended for long-term administration, as is the case for rheumatologic indications, it is recommended that immunogenicity data be acquired over at least 1 year. If immunogenicity findings are to be extrapolated from one disease to additional indications, the subjects being studied should be those most likely to develop antidrug antibodies, such as patients not receiving concomitant immunosuppressive medications. For instance, infliximab-dyyb and adalimumab-atto were studied as monotherapy in ankylosing spondylitis (AS) and psoriasis, respectively (19,20). The nature of the antidrug antibodies (e.g., neutralizing versus non-neutralizing) and the relative magnitude of the immune responses to the biosimilar and its reference product were assessed in order to characterize the immunogenicity risk and determine the clinical relevance of the antidrug antibodies. Any candidate biosimilar that is found to be more immunogenic than its reference product will fail to meet criteria for biosimilarity (10).

Importantly, a biosimilar found to be less immunogenic than its reference product may be approved, provided that a subset analysis of clinical trial subjects who did not develop antidrug antibodies reveals comparable efficacy and safety. For example, among patients with rheumatoid arthritis (RA) treated through 24 weeks, antidrug antibodies were observed in 13.1% of those receiving reference etanercept but in only 0.7% of those receiving the biosimilar etanercept SB4 (21). There was a modest effect of antidrug antibodies on reducing trough drug levels, but this had no significant effect on efficacy or safety. This was most likely due to the transient expression of these antibodies (22). SB4 (etanercept) is now marketed as Benepali in the European Union (EU) and as Brenzysin in South Korea, but it is not available in the US.

As methods to detect molecular changes associated with drift and evolution have improved, assays to detect antidrug antibodies have evolved over time to become more sensitive. In early studies of therapeutic monoclonal anti-TNF antibodies, antidrug antibodies were identified in only a small proportion of subjects (~8–12%) (23,24). This low detection rate was due primarily to the inability of assays to measure antidrug

antibodies in the presence of the drug. In recent clinical trials, antidrug antibodies have been detected in a larger proportion of patients, using acid dissociation to allow measurement of antidrug antibodies in the presence of the drug, along with a more sensitive bridging enzyme-linked immunosorbent assay (25). In the PLANETRA trial, antidrug antibodies were detected in 48% of patients receiving reference infliximab and in an identical proportion of those treated with the biosimilar (infliximab-dyyb), through 30 weeks of treatment (26). In the clinical trial comparing adalimumab-atto to reference adalimumab, the frequency of antidrug antibodies was similar in both groups of patients though 26 weeks (38%), as was the incidence of neutralizing antidrug antibodies (11.1% with reference adalimumab versus 9.1% with biosimilar) (20). In summary, the frequency of binding and neutralizing antidrug antibodies has been similar between biosimilars approved in the US to date and their reference products, and there have been no signals to suggest a differential effect of antidrug antibodies on efficacy, safety, or patient outcomes between biosimilars and their reference products.

An important implication of the comparative immunogenicity studies carried out to date is that a patient who develops antibodies to a reference drug with resultant loss of clinical response should not be switched to its biosimilar. This recommendation is based on the finding that antidrug antibodies to a reference product cross-react with its biosimilar, as shown in studies of infliximab-dyyb conducted in RA, AS, and inflammatory bowel disease (IBD) patient groups (27,28). Thus, patients in whom loss of efficacy is attributable to antidrug antibodies directed against a reference drug or its biosimilar should subsequently receive an unrelated therapeutic agent. Whether multiple switches between a reference drug and various biosimilars might result in increased immunogenicity has not yet been studied adequately. However, the EGALITY study (29), which compared the biosimilar etanercept-szszs to reference etanercept, included 3 switches between the 2 products (each of 6 weeks' duration), and demonstrated no loss of efficacy or increase in adverse events with repeated switching, compared to continued treatment without switching.

Postmarketing pharmacovigilance using observational registry data will be critical to assess the effect of switching on immunogenicity. The FDA and the EMA require both manufacturers of reference biologics and manufacturers of biosimilars to conduct the same postmarketing pharmacovigilance after any manufacturing change (30). Enrollment of biosimilars-treated patients into registries, such as the Rheumatology Informatics

System for Effectiveness (the registry of the American College of Rheumatology [ACR] [31]) and the pediatric registry sponsored by the Childhood Arthritis and Rheumatology Research Alliance in the US, along with comprehensive spontaneous adverse event reporting in both adults and children, should facilitate detection of any loss of efficacy or toxicity as signals of clinically significant immunogenicity.

### **Extrapolation of indications, switching, and substitution and interchangeability**

**Extrapolation of indications.** When a biosimilar is approved by the FDA for use in one indication, it may be approved simultaneously in any or all of the other indications for which the reference product has been approved, without the requirement for clinical trial data from each disease. This process, which is known as “extrapolation of indications,” eliminates the costs and delays introduced by the need to replicate other previously successful phase III randomized controlled trials that had been conducted with the reference product. The FDA and EMA have provided guidelines for justification of extrapolation of indications for biosimilars (10). Once a biosimilar has met criteria for approval, the cumulative experience with its reference product can be applied to justify extrapolation of the approval of the biosimilar to those other indications in which it was not initially studied.

For example, the infliximab biosimilar infliximab-dyyb (referred to as CT-P13 during its development) was evaluated extensively in comparison to reference infliximab (Remicade) using functional assays such as complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and Fc $\gamma$  receptor III binding. The results of these tests showed this biosimilar to be highly similar to infliximab, according to statistical parameters established by the FDA (32). Infliximab-dyyb was then compared to reference infliximab in randomized clinical trials in RA (the PLANETRA trial), in combination with methotrexate (MTX), and in AS without concomitant MTX (the PLANETAS trial). The PLANETAS study demonstrated equivalent pharmacokinetic parameters and similar clinical outcomes, and the PLANETRA study demonstrated equivalent efficacy. In both studies, safety and immunogenicity of the biosimilar were comparable to those of the reference product (19,33).

Data from the preclinical analytical and functional studies, along with the results of the clinical trials, supported FDA approval of infliximab-dyyb with extrapolation to all other diseases for which reference infliximab had already been approved, but which were no longer

protected by exclusivity. Similar data on the adalimumab biosimilars BI 695501 (adalimumab-adbm) and ABP 501 (adalimumab-atto), for the etanercept biosimilar GP2015 (etanercept-szszs), and for the infliximab biosimilars SB2 (infliximab-abda) and infliximab-qbtx (PF-06438179/GP1111) (5) resulted in extrapolation to all nonexclusive indications for which the respective reference products had been approved (29,34–37).

Although none of the biosimilars approved to treat rheumatologic and other inflammatory diseases has been studied in children, several have been approved for pediatric indications by extrapolation. In the US, infliximab-dyyb, infliximab-abda, and infliximab-qbtx are all approved for treatment of pediatric Crohn’s disease. In the EU, infliximab-dyyb and infliximab-abda are both approved for treatment of pediatric Crohn’s disease and pediatric ulcerative colitis. The adalimumab biosimilars adalimumab-adbm and adalimumab-atto and the etanercept biosimilar etanercept-szszs are both approved for treatment of polyarticular juvenile inflammatory arthritis. The benefits and risks of using biosimilars to treat children likely are similar to those in adults. However, since children frequently metabolize drugs, including biologics, more rapidly than adults, it may be important to conduct pharmacodynamic and pharmacokinetic studies in children. The FDA encourages manufacturers to study biosimilars in the pediatric population during product development (38). After approval, postmarketing surveillance of biosimilars should be conducted in children and adolescents as well as in adults, since potential immunogenicity may be of particular importance in these younger patients with chronic diseases, who might be exposed to several biologic agents during their lifetime.

Extrapolation continues to be an area of uneasiness among clinicians, who are surprised to find that a biosimilar may be approved for an indication, such as IBD, in the absence of clinical trials conducted in those patient populations (39,40). Indeed, lack of confidence among clinicians in extrapolation of indications may limit acceptance of biosimilars in geographic areas where utilization is not mandatory. To date, however, “real-world” controlled trials such as NOR-SWITCH (41), registry studies such as DANBIO (42), and preliminary results of a postmarketing 54-week randomized clinical trial in Crohn’s disease (43) have demonstrated the efficacy and safety of biosimilar infliximab-dyyb to be comparable to those of reference infliximab in a range of diseases, providing reassuring evidence to support regulated extrapolation of indications for biosimilars.

**Substitution and interchangeability.** Changing from one biologic to another due to inadequate efficacy or side effects, as directed by a provider in partnership with

the patient, occurs commonly and requires that the provider write a new prescription. “Substitution” is the FDA-preferred term to describe a change made by someone other than the prescriber (such as a pharmacist) and is regulated by state law. Non-medical substitution (also known as payor substitution) refers to a change imposed on a medically stable patient for reasons unrelated to a drug’s efficacy or tolerability in that patient. Insurance companies and pharmacy benefits managers (PBMs) (third-party administrators of prescription drug programs for commercial, government, and self-insured employer plans) play important roles in non-medical substitution. Such changes in therapy typically are made in response to insurance company or PBM policies that determine which biologics are “preferred” (almost always due to cost) and therefore preferentially covered by the patient’s insurance plan.

“Interchangeability” is a status that may be granted to a biosimilar under the 351(k) pathway that would allow for substitution (1). To be designated as interchangeable, a biosimilar must be “expected to produce the same clinical result as the reference product in any given patient.” In addition, “if administered more than once to an individual,” the risk of developing an adverse event or diminished efficacy with alternating between the reference product and the biosimilar must not be “greater than the risk of using the reference product without such alteration or switch” (1).

In January 2017, the FDA published draft guidance regarding demonstration of interchangeability of an already approved biosimilar with its reference product (44). The FDA proposes relying on postmarketing pharmacovigilance data, as well as data derived from at least 1 prospective, controlled switching study, comparing treatment with the reference product alternating with the biosimilar to continuous treatment with the reference product. Such a clinical trial should consist of an initial “lead-in” period during which all subjects are treated with the reference product, followed by a period during which subjects are randomized either to the switching arm or to receive continuous treatment with the reference product. In the switching arm, subjects would be crossed over at least 3 times to the alternative product (e.g., reference product to biosimilar to reference product to biosimilar). Pharmacokinetic measures, such as maximum drug concentrations and area under the curve from the infusion/injection until the end of the dosing period, should serve as the primary end points for such studies. Secondary end points should include other pharmacokinetic measures (trough drug concentrations and time to reach maximum concentration) and assessments of efficacy, safety, and immunogenicity. The FDA prefers that the comparator used in such studies be a reference product that is

licensed in the US. It should be noted that the biosimilar product has already undergone substantial preclinical analyses (Figure 2).

To date, the interchangeability pathway has not been finalized; thus, no manufacturer has sought, and no biosimilar has been granted, the designation “interchangeable.” However, in anticipation of future availability, most states and the territory of Puerto Rico have passed laws regulating the substitution of interchangeable biosimilars (45), and several more states are in various stages of enacting similar legislation.

While interchangeability laws vary somewhat by state, the majority preserve the prescriber’s right to prevent automatic substitution by writing “dispense as written” or “brand medically necessary” on the prescription. In some states, the prescriber must be notified of any allowable substitution made at a pharmacy. Notification laws vary and grant pharmacies anywhere from <24 hours to >10 days to make prescribers aware of a change. In 4 states, legislated provider notification rules carry “sunset” provisions, stipulating that the statutes expire automatically after a specific date unless they are renewed; in Virginia, the law already has expired. Some states require that the patient be notified if a biosimilar has been substituted for the prescribed drug, that the patient must consent to the substitution, or that the pharmacist must explain to the patient the difference in wholesale acquisition cost between the reference biologic and the biosimilar. Pharmacists (and, in some states, providers) must retain records of substituted biologic medications, and the state pharmacy board must maintain a public list of medications for which interchange is permissible.

**Transitioning and changing.** Changing to a biosimilar is an intentional therapeutic alteration that is initiated by a health care provider in partnership with the patient. Such a change often is made for economic reasons, since a biosimilar usually costs less than its reference product. However, this change may be made for medical reasons when a patient is not responding adequately to a drug other than the reference product and the biosimilar is chosen as the alternative treatment because of its lower cost. The term “switching” is used in the BPCI Act when referring to transitioning to or from a biosimilar which has been designated as “interchangeable.”

Clinical trials comparing biosimilars to their reference products typically include an open-label extension, during which subjects who were treated initially with the reference drug are transitioned to the biosimilar for the remainder of the study. The efficacy and safety of the biosimilar among subjects who transitioned from the reference product are compared to the efficacy and safety among those who received the

biosimilar throughout the trial. In open-label extensions of the PLANETAS study and the PLANETRA study, transitioning to the biosimilar infliximab-dyyb (CT-P13) after 54 weeks of treatment with reference infliximab did not result in a loss of efficacy or an increase in adverse events or immunogenicity (33,46). Comparable results have been observed in the open-label extensions of other studies (47,48), as well as in postmarketing observational studies (36,43,49–56).

Transitioning from a reference drug to its biosimilar was studied prospectively in NOR-SWITCH, a 52-week randomized, double-blind, noninferiority, phase IV clinical trial comparing the effect of transitioning from reference infliximab to the biosimilar infliximab-dyyb (CT-P13) versus continuation of treatment with reference infliximab in various approved indications (41). This study included 482 patients with RA, spondylarthritis, psoriasis, psoriatic arthritis, Crohn's disease, or ulcerative colitis, each of whom had been treated with a stable dose of reference infliximab for at least 6 months. The primary end point was worsening in disease-specific composite measures and/or agreement between the investigator and the patient that increased disease activity necessitated a change in treatment by week 52. The NOR-SWITCH trial demonstrated noninferiority (using a margin of 15%) of transitioning from the originator biologic to the biosimilar for the aggregate group of patients with the various diseases. Safety and immunogenicity were comparable between the 2 treatment arms. However, the study did not have sufficient statistical power to compare the treatment approaches among patients with any individual disease.

We expect that transitioning and non-medical substitution will become as common in the US as it has in Europe and the rest of the world. Based on clinical trial and “real-world” observational data on transitioning between reference products and biosimilars, and on our understanding of product drift, we do not expect that there will be issues regarding efficacy and safety. However, we encourage vigorous postmarketing surveillance of both biosimilars and their reference products as we enter the era in which patients may undergo multiple changes as a result of insurance company and PBM formulary preferences.

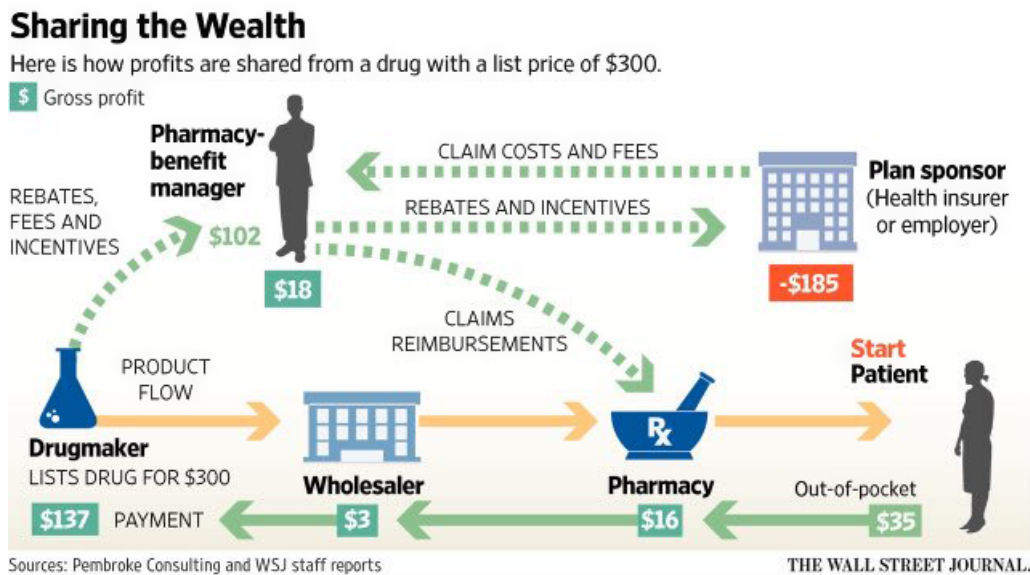
### **Economics of biosimilars and patient access**

One final consideration in the use of biosimilars is economic—particularly, economic issues affecting patient access to these agents. The only anticipated advantage of a biosimilar over its reference product is lower cost, since the 2 drugs should otherwise be therapeutically equivalent. The degree to which the

availability of biosimilars in the US will drive down the cost of biologic therapy, and who will benefit from any cost reductions, remain to be seen. There are many ways to measure cost differences of a biosimilar compared to its reference product; a discussion of these methods is beyond the scope of this report. However, multiple variables affect the price of biosimilars. The first US biosimilar relevant to rheumatology, infliximab-dyyb, debuted at a 15% discount compared to reference infliximab, a reduction that was congruent with a 2009 Federal Trade Commission prediction (57). Subsequent price reductions could be realized eventually if competition from the second and third FDA-approved infliximab biosimilars, infliximab-abda and infliximab-qbtz, becomes significant.

Insurance companies and PBMs will continue to play key roles in determining the economic impact of biosimilars. Currently, PBMs negotiate contracts with manufacturers, settling on a purchase price that is further moderated by rebates given to the PBM by the manufacturer according to sales volume and/or market share (Figure 3). Paradoxically, this system could prevent significant reductions in the cost of biologics in the US, or even drive prices higher, due to incentives that profit PBMs: manufacturers have the ability to increase rebates in order to earn a more favorable status on the PBM's formulary, and PBMs charge administrative fees to insurers based on drug prices (58). If the actual cost of a reference product were lowered to below the average wholesale cost of its biosimilar by discounts and rebates provided to PBMs by manufacturers, then the biosimilar's cost advantage would be eliminated and biosimilar sales might effectively be stifled. Were biosimilars to disappear from the market, there no longer would be pressure on reference product manufacturers to lower prices, and the cost of treating patients would increase. Thus, biosimilars play an important role in maintaining a competitive marketplace to keep drug prices under control.

Even under ideal circumstances, it will likely take several years for overall savings to the US health system from the use of biosimilars to be realized, due to multiple factors. First, the price of originator biologics increased substantially in the 6 years between Congressional authorization of the biosimilar approval pathway and approval of the first biosimilars (e.g., the price of reference infliximab [Remicade] increased by 63%) (59). This is similar to the 50% increase in the price of Lipitor that occurred over the 6 years prior to its patent expiration (60). Because the first biosimilars in the US (filgrastim-sndz and infliximab-dyyb) were priced at only 15% less than their reference products, robust competition will be needed for substantial price



**Figure 3.** Model showing the estimated distribution of revenues from the sale of a hypothetical brand-name drug with a list price of \$300. Estimated dollars gained and lost in transactions between entities are shown. The cost of the drug to the payor is influenced by rebates and incentives that are negotiated by the pharmacy benefit manager. Such rebates and incentives can be based on the price of the drug and thereby may serve as a perverse incentive to keep drug prices high. The sum of payments does not equal the gross profits, in part because of markups and discounts taken during the filling of a prescription. Reprinted by permission of the *Wall Street Journal*. Copyright © 2017 Dow Jones & Company, Inc. All rights reserved worldwide. License number 4216541060693.

reduction. This competition could come about when multiple biosimilars for a reference product become available, or if a biosimilar is approved as being interchangeable and is substituted by pharmacists for its reference product or other biosimilars.

To incentivize the use of biosimilars, commercial and government insurance programs could harmonize drug prices with patients' out-of-pocket costs and provider reimbursement. Currently, however, patients with commercial insurance are likely to have similar copayments for both biosimilars and originator biologics, due to PBM- or plan-mandated patient cost sharing. Also, patients' out-of-pocket costs for biosimilars in the

Medicare Part D (self-administered drug) program likely will be higher than for originator biologics due to a flaw that maintains, rather than reduces, patient cost-sharing in the coverage gap (also known as the "donut hole") for biosimilar treatments until 2020 (61).

Finally, on November 2, 2017, the Centers for Medicare and Medicaid Services (CMS) announced a policy change regarding reimbursement of provider-administered biosimilars under Medicare Part B (62). Effective January 1, 2018, different biosimilars of the same originator biologic will be assigned individual billing codes. Under the prior CMS policy, established in 2016, biosimilars of a common originator biologic were grouped under a single

**Table 1.** Resources for health care providers to educate themselves and inform their patients\*

Title or description	Web site
American College of Rheumatology Position Statement on Biosimilars	<a href="https://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf">https://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf</a>
American College of Rheumatology Responds to FDA Draft Guidance on Biosimilar Interchangeability	<a href="https://www.rheumatology.org/About-Us/Newsroom/Press-Releases/ID/810/American-College-of-Rheumatology-Responds-to-FDA-Draft-Guidance-on-Biosimilar-Interchangeability">https://www.rheumatology.org/About-Us/Newsroom/Press-Releases/ID/810/American-College-of-Rheumatology-Responds-to-FDA-Draft-Guidance-on-Biosimilar-Interchangeability</a>
FDA information on biosimilars	<a href="https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/">https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/</a>
Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book)	<a href="https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm">https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm</a>
Tips, Resources to Help Rheumatologists Educate Patients on Biologics and Biosimilars	<a href="http://www.the-rheumatologist.org/article/tips-resources-help-rheumatologists-educate-patients-biologics-biosimilars/">http://www.the-rheumatologist.org/article/tips-resources-help-rheumatologists-educate-patients-biologics-biosimilars/</a>

\* FDA = Food and Drug Administration.



Healthcare Common Procedure Coding System billing code and reimbursed based upon the weighted average sales price of those biosimilars. The change represents an attempt by CMS to encourage licensing of more biosimilar products, incentivize market competition, and enhance long-term cost savings.

Of note, discounts for biosimilars in the US are smaller than those in countries with single-payor models. For example, the public sectors in Denmark and Norway have purchased biosimilar infliximab-dyyb at a 60–70% discount relative to the cost of reference infliximab (63). This results from the ability of these governments to leverage purchasing power through large-scale use of the biosimilar. In the US marketplace, competition may be reduced by relatively modest initial uptake of the biosimilar and the limited purchasing power of individual payors, compared to that of a larger single payor.

Growing public interest in ways to reduce high drug prices is reflected by more frequent inquiries by journalists, economists, regulators, and legislators, regarding the mechanisms that promote inflation in the pharmaceutical market. This public interest, advocacy by groups supporting availability of these drugs through affordable pricing, and the passage of appropriate legislation to regulate drug prices could help to reduce the financial burden placed on patients receiving these and other expensive medications.

### Additional considerations

ACR position statements and comments are revised periodically. Those pertaining to biosimilars will be updated as the relevant scientific and regulatory aspects evolve and as they become integrated into clinical practice. The initial position of the ACR on biosimilars supported the rationale behind pursuing biosimilars, but urged caution as they were being developed, evaluated, and approved. Now that biosimilars have been used successfully in Europe, with rigorously acquired data supporting their broader use, and as the US is on the verge of a similar transition, the ACR is poised to reconsider its position. During this period of transition, it is reassuring to recognize the scientific rigor with which the FDA and other regulatory agencies around the world have evaluated biosimilars. Health care providers should now incorporate biosimilars, where appropriate, into regimens to treat patients with rheumatologic diseases. It is important to maintain a working knowledge of approved biosimilars and to monitor evolving policies and guidelines regarding the development and use of new biosimilars. Table 1 lists selected resources available for health care providers and

patients, including a link to the latest ACR statement on interchangeability of biosimilars.

Communication between providers, pharmacists, and patients will be critical to alleviate anxiety and reduce skepticism regarding the use of these newly available agents. We remain optimistic that the use of biosimilars will improve patient access to biologic agents, allowing continued delivery of high-quality health care to be realized at a lower cost to the individual patient.

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### AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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