REVIEW ARTICLE

Biosimilars for Immune-Mediated Chronic Diseases in Primary Care: What a Practicing Physician Needs to Know

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ABSTRACT

The introduction of biologics has revolutionized the treatment of immune-mediated diseases, but high cost and limited patient access remain hurdles, and some physicians are concerned that biosimilars are not similar enough. The purpose of this narrative review is to describe biosimilar safety, efficacy, nomenclature, extrapolation and interchangeability. In the United States, the Biologics Price Competition and Innovation Act created an abbreviated pathway for licensing of a biologic that is biosimilar to another licensed product (i.e., the reference product). This approval pathway differs from that of generic small-molecule drugs because biologics are too complex to be perfectly duplicated, and follows a process designed to demonstrate that any differences between the biosimilar and its reference product have no significant impact on safety and efficacy. The US approval process requires extensive analytical assessments, animal studies and clinical trials, assuring that biosimilar products provide clinical results similar to those of the reference product.

Key Indexing Terms: Biologic; Biosimilar; Immunology; Rheumatology. **[Am J Med Sci 2018;355(5):411–417.]**

INTRODUCTION

Immune-mediated chronic diseases have a significant direct and indirect burden on patients and society.[1] The first biologic agent for rheumatoid arthritis was introduced to the market in the late 1990s.[2] Since then, biologics have revolutionized not only the treatment of rheumatoid arthritis,[3] but also of moderate to severe psoriasis,[4] inflammatory bowel disease[5,6] and other conditions.[7-9] Whereas conventional disease-modifying drugs have improved the prognosis for patients, biologics have further enhanced symptom management and slowed disease progression for those with challenging conditions, owing to their high efficacy, speed of onset and tolerability profile.[10,11] However, these agents come with a high cost; biosimilars may help reduce that cost.

A biosimilar is designed to be highly similar to the innovator biologic (i.e., reference product). However, because of their complexity, biologics cannot be duplicated. A biosimilar is designed to have the same target-binding characteristics as the reference product. An established regulatory pathway for the approval of biosimilars has been in place in the European Union since 2005.[12] The European Medicines Agency (EMA) approved the first biosimilar in 2006 (Omnitrope [somatostatin]) and the first biosimilar monoclonal antibodies in 2013 (the infliximab biosimilars, Remsima and Inflectra).[13] The Biologics Price Competition and Innovation Act was introduced in 2009 and created an abbreviated pathway for licensing of a biological product that is biosimilar to a reference product in the United States.[14] The Biologics Price Competition and Innovation Act has major implications for the US healthcare system.[15] Zarxio (filgrastim-sndz[16]), a biosimilar of Neupogen (filgrastim), was the first product approved by the US Food and Drug Administration (FDA) via this abbreviated pathway in March 2015; approval was granted for the same indications as the reference product. As of this writing, the FDA has approved 6 additional biosimilars—Inflectra (infliximab-dyyb[17]) and Renflexis (infliximab-abda[18]), both biosimilars to Remicade (infliximab); Erelzi (etanercept-szzs[19]), a biosimilar to Enbrel (etanercept); Amjevita (adalimumab-atto[20]) and Cyltezo (adalimumab-adbm[21]), both biosimilars to Humira, and Mvasi (bevacizumab-awwb),[22] a biosimilar of Avastin. However, some of the newer biosimilars may not be available in the United States immediately owing to the complexity of intellectual property and patent issues. As such, Amgen's Amjevita launch in the United States will be delayed until 2023, as outlined in a recent patent settlement with AbbVie[23]; Cyltezo is not commercially available at this time[24]; and Mvasi is not expected to be available until at least 2019.[25]

This review will discuss how biosimilars are different from small-molecule generics and the quality assurances

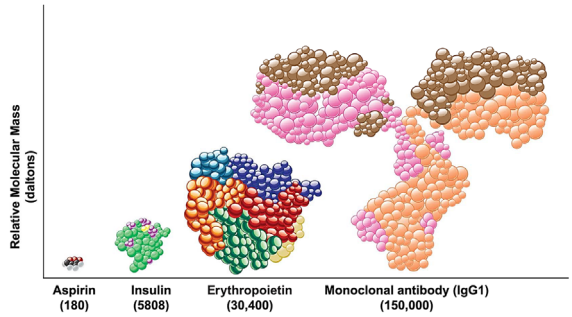

FIGURE 1. Structural comparison of a small-molecule drug (e.g., aspirin) and biologic products. Monoclonal antibodies have a structure that is more complex than small-molecule agents and lower molecular-weight biologics. Reprinted from European Journal of Cancer, vol. 11, Mellstedt H, Clinical considerations for biosimilar antibodies, 1-11, Copyright (2013), with permission from Elsevier.[26]

required to ensure a place for biosimilars in the treatment of chronic immune-mediated diseases in the United States.

DIFFERENCES BETWEEN BIOLOGICS AND THEIR BIOSIMILARS AND SMALL-MOLECULE DRUGS AND THEIR GENERICS

To understand how biosimilars are different from traditional generic drugs, we first need to understand how biologics are different from small-molecule drugs (Figure 1).[26] Older therapeutics such as aspirin and oral antihypertensive agents are small compounds with well-defined chemical structures, low molecular weights and a reproducible manufacturing process. The active moiety of a generic drug is structurally identical to that of the original reference product. In comparison, biologics are large, complex molecular entities with critical tertiary and quaternary structures, produced using living cell cultures. This process involves expression of the drug in bacteria, yeast or mammalian cell lines, followed by extraction and purification, and is subject to inherent variability and molecular heterogeneity.[27] Additionally, biologics often undergo posttranslational modifications, such as glycosylation.[27] Thus, unlike chemically synthesized generic small-molecule drugs, biosimilars are highly similar to, but never exact copies of, the biologic reference product. Equally important, every batch of a reference product consists of multiple variants that may change from batch to batch.

The approval process for an original product, whether a biologic or a small-molecule drug, begins with drug development, moves through the preclinical phase and continues to clinical testing (Table).[28] Phase 1 studies, conducted in a small number (20-100) of healthy volunteers or patients, assess the safety of a drug and evaluate the drug's absorption, distribution, metabolism and excretion. Phase 2 studies are conducted in a few hundred patients, are randomized and provide a more detailed picture of a drug's optimal dose as well as efficacy and safety. Phase 3 studies are double-blind, randomized studies in a large number of patients (300-3,000) and assess efficacy and safety versus the current standard of care in the disease state of interest.[29] For an indication of a biologic or a small molecule, the FDA typically requires 2 well-controlled phase 3 clinical trials.

In comparison, the approval of generic small-molecule drugs is based on structural and pharmacokinetic bioequivalence to the original brand-name product (Table). Because the generic products have a molecular structure identical to that of the original product, they only need to be tested in a phase 1 study to demonstrate bioequivalence prior to approval.[28] The study needs to demonstrate that the extent and rate of drug exposure are within reference limits mandated by the FDA. This means that the 90% CIs for the area under the concentration-time curve and the maximum observed plasma concentration would be within 80-125%.[14] In contrast, the approval process for a biosimilar developed as an alternative treatment option for an existing biologic requires more steps than generic drug approval, but fewer clinical trials than required for reference products.

According to the FDA approval process, a biosimilar is a biologic that is highly similar to its reference product,

TABLE. Comparison of generic small-molecule and biosimilar drugs.[30,40,68–70]

	Generic small-molecule	Biosimilar
Molecular size and structure	Low molecular weight	Large polypeptide or protein
	Single molecule	Heterogeneous mixture
Structure compared with reference product	Identical	Similar, cannot be identical
Immunogenic	Very rare, although allergic reactions are possible	High possibility of antidrug antibody formation
Production/manufacturing	Chemical synthesis	Biotechnological synthesis, highly process-dependent
Approval process	Abbreviated, bioequivalence study	Abbreviated, analytic studies, animal studies, at least 1 phase 3 clinical study
Pharmacovigilance	FDA Adverse Event Reporting System (active surveillance, spontaneous event reporting)	FDA Adverse Event Reporting System (active surveillance, spontaneous event reporting)

FDA, Food and Drug Administration.

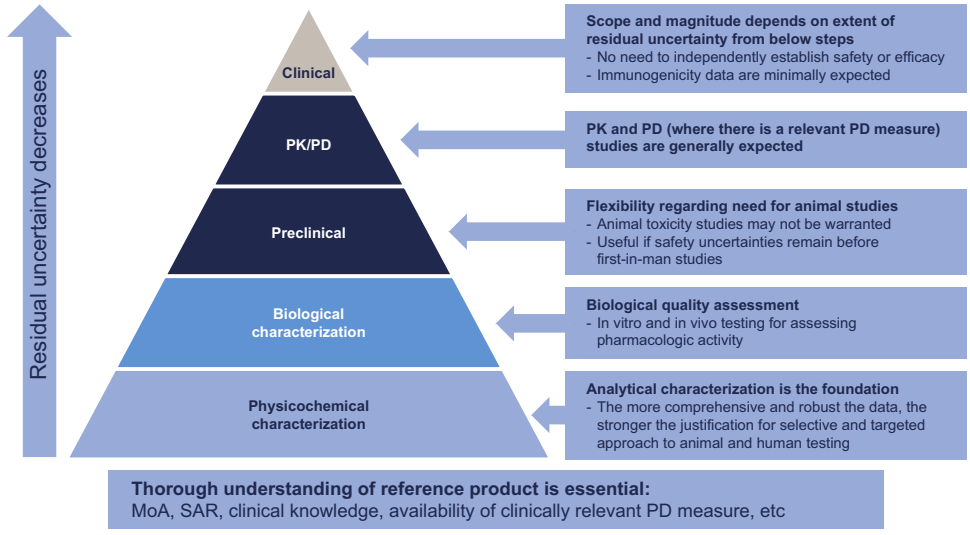

FIGURE 2. Overview of the US Food and Drug Administration stepwise approval process for biosimiliars. Reprinted with permission of the American Society of Nephrology, from The approval process for biosimilar erythropoiesis-stimulating agents, Wish JB, 9(9) 2017. MoA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics; SAR, structure-activity relationship.

allowing for minor differences in clinically inactive components,[30,31] but there must be no clinically meaningful differences between the biosimilar and the reference product it was compared to in terms of safety, purity and potency (Figure 2).[32] The studies involved in this regulatory process provide much greater evidence of similarity between a biosimilar and its reference product than what is available for the different batch-to-batch variants in the reference product.[33] If a biosimilar product has target-binding characteristics, pharmacokinetic properties and immunogenicity similar to the innovator, it will most likely function like the reference product in clinical trials as well.[34]

Sources of Differences in Biosimilar Manufacture

The inability to produce identical copies of a biologic reference product, especially glycoproteins such as antibodies, is a consequence of the complex biochemical structure of large proteins and the inherent variability in their production.[27,35] The manufacture of both reference products and biosimilars requires the synthesis of proteins using a genetically modified organism as an expression system; development involves cloning and expressing the requisite gene sequence in the system of choice, which undergoes culture or fermentation before the final product is purified.[27] Variables that may affect product similarity include the incubation conditions; bacterial, yeast or mammalian cell expression system; excipients; manufacturing-specific impurities and batch-to-batch variation.[14] Microheterogeneity, i.e., batches consisting of a mix of nonidentical molecules, is a normal feature of biotechnology.[36] Additionally, changes to the manufacturing process within a production facility, such as advances in technology, changes in raw material suppliers or increases in production scale, can result in batch variation, as can a switch to a different production facility.[37,38] For the adalimumab reference product approximately 20 manufacturing changes have been documented over the course of a decade. Testing of more than 500 batches has shown that key physicochemical and functional quality attributes of the adalimumab reference product have remained within a narrow range over time.[37] In contrast, a characterization of rituximab batches revealed an abrupt change in 2008, with marked changes of the N- and C-terminal heterogeneity and variation in antibody-dependent cellular cytotoxicity. The magnitude and suddenness of these effects suggested manufacturing process changes.[39]

For proprietary reasons, publicly available information regarding the precise manufacturing process for any given biologic product is limited.[27] Comparability of the specific manufacturing processes used in the production of a biosimilar and its reference product is not a requirement of regulatory authorities in the European Union or United States.[13] The FDA offers specific guidance on quality variables that may affect biosimilarity and should be considered in the manufacturing process.[40]

BIOSIMILAR QUALITY ASSURANCE

The FDA requirements begin with extensive structural and functional characterization of the proposed biosimilar and its reference product (Figure 2). Three key characteristics of biologics potentially associated with qualitative differences in a biosimilar product are: (1) posttranslational modifications, (2) 3-dimensional structure and (3) protein aggregation.[41] Therefore, analytical testing is undertaken to compare protein content,

activity, stability, impurities and immunogenicity.[35,42] Structural analytical testing assesses a molecule for the primary amino acid sequence; the primary, secondary, tertiary and quaternary structure; posttranslational modifications, such as glycosylation and phosphorylation and other modifications, including protein deamidation and oxidation. Many of these characteristics can be determined using liquid chromatography, mass spectrometry, microcapillary electrophoresis and analytical ultracentrifugation. The extent to which these preclinical assessments are able to identify qualitative or quantitative differences in product attributes, including the reference product, its excipients and any impurities, will determine what additional studies are needed.[35] The overall assessment involves the totality of evidence, including structural and functional characterization, nonclinical evaluation, clinical pharmacokinetic and pharmacodynamic data, clinical immunogenicity data and efficacy and safety studies.[30] Thus, biosimilarity may be demonstrated even in cases when a biosimilar and its reference product show minor structural differences, provided these differences are not clinically meaningful in terms of safety, purity and potency.

EXTRAPOLATION AND INTERCHANGEABILITY

One consideration in biosimilar licensing includes the validity of extrapolating clinical data from 1 condition to support additional indications for which the reference product is approved (e.g., rheumatoid arthritis to inflammatory bowel disease).[43,44] Both the FDA and EMA accept extrapolation, provided it is scientifically justified.[45] This was the case with the approval of the biosimilar infliximab in the European Union, with the EMA permitting extrapolation to all 8 approved indications of the originator product based on extensive preclinical data and demonstration of similar efficacy and safety in 1 disease.[33,46] Similarly, the FDA approved the infliximab biosimilar Inflectra (infliximab-dyyb)[17] for 7 eligible indications, based on the Arthritis Advisory Committee recommendation for extrapolation.[47] Although some physicians may question whether 1 clinical trial in another disease state is sufficient evidence to support extrapolation, different batches of the innovator are also not identical, yet we readily extrapolate their safety and efficacy without any clinical trial evidence.

Another emerging area of biosimilar licensing is the formal designation of interchangeability; unlike the EMA, the FDA permits a formal designation for a biosimilar and its FDA-licensed reference product.[48,49] The US standard for "interchangeability" is more rigorous than that for "biosimilarity." The application for such an interchangeable biologic product must be sufficient to show that the product "can be expected to produce the same clinical result as the reference product in any given patient."[50] In January 2017, the FDA released draft guidance indicating that interchangeable applications will need to include a switching study or studies with multiple switches; although postmarketing data may be included in these applications, postmarketing data alone will not suffice.[50] Notably, interchangeability between different batches of a reference product are not held to this same standard, even though different batches of a reference product are not identical.

A product that meets FDA interchangeability standards could subsequently be substituted at the pharmacy level for a reference product without the intervention of the healthcare provider (i.e., the patient may receive the biosimilar instead of the reference product, even if the physician wrote the prescription for the reference product). Over the last 5 years, bills or resolutions related to biologics and biosimilar substitution have been filed in 37 states; currently 27 states and Puerto Rico have signed these into law.[51] The cornerstone of these laws is that the biologic product first be approved as "interchangeable by the FDA, with variations regarding patient and provider notification based on state jurisdiction."[51] Again, this standard does not apply to different batches of innovator products, despite the variations between those batches.

Finally, pharmacovigilance is important for extrapolation of indication and interchangeability.[52,53] In the United States, this usually takes the form of spontaneous adverse event reporting. A key to such is accurate identification of the product taken by the patient; thus distinguishable names would be needed for reference products as well as biosimilars. Note, however, that each batch of a biologic—reference or biosimilar—will have some variability and not be identical to another batch. Each batch is not required to have a different name, but batch numbers could be used for reporting without the need for different generic names for the products.

IMMUNOGENICITY

All biologic drugs have the potential to be immunogenic in that they may induce an immune response that stimulates the production of antidrug antibodies.[54] Immunogenicity may be associated with reduced clinical efficacy and increased risk of adverse events. A patient's immune response may vary based on genetic make-up, immunologic condition (patients with rheumatoid arthritis are more susceptible to the development of immunogenicity than those with other diseases),[55] dose and mode of administration (subcutaneous administration is more immunogenic than oral or intravenous administration). A recent study in 250 patients with rheumatoid arthritis and spondyloarthritis on infliximab, and 77 controls, demonstrated that 50% of patients treated with infliximab developed anti-infliximab antibodies, and of those, 100% also exhibited antibody reactivity against the biosimilar (CT-P13).[56] Thus, switching patients who are not responding to the reference product because of antibody development to the biosimilar will likely not resolve the loss of response.

Another unanswered clinical issue relates to switching a patient's treatment multiple times from biosimilar A to biosimilar B (from a different company) to biosimilar C (another different company) and then back to A, whether driven by insurance coverage or formulary decisions. Note, however, that the same problem already occurs with switching between batches of the innovator product. Patients may be taking 1 batch, then switch to another, then switch back or, potentially, to a third. There is variability between batches, with much less information than biosimilars offer to show similarity. The introduction of biosimilars does not raise a new issue of switching; the uncertainty associated with switching is already an issue, one that we accept (or ignore).

BIOSIMILAR NOMENCLATURE

The FDA naming approach used for several biologics (not biosimilars) includes adding a prefix to a common root international nonproprietary name to distinguish among products or manufacturers (e.g., tbo-filgrastim [Granix, Teva Pharmaceuticals USA Inc.],[57] ziv-aflibercept [Zaltrap, Regeneron Pharmaceuticals, Inc/Sanofi-aventis U.S. LLC]).[58] Although the FDA approved the first biosimilar filgrastim with a distinguishable suffix to identify the manufacturer (filgrastim-sndz), the recent FDA naming guidance states that the nonproprietary name (i.e., generic name) designated for a biosimilar product will be a "proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of 4 lowercase letters".[59] Subsequent biosimilar approvals in the United States, such as the one for adalimumab-atto, have followed this convention. In contrast, the Medicines in Europe Forum and the International Society of Drug Bulletins have taken a more pragmatic position regarding naming convention. They contend that the assignment of a different international nonproprietary name from that of the reference product would lead to a profusion of names for the same drug, causing confusion among healthcare professionals and patients.[60] However, biosimilars and their reference products can still be differentiated using their commercial brand names, which are frequently used to refer to the products, and may be used to report adverse events. Moreover, each batch of a biologic is different from the previous, and different names are not required for differentiation.

From a patient perspective, it will be crucial for a healthcare provider who offers a biosimilar drug in place of its reference product to carefully explain how the safety, efficacy and potency of the biosimilar product compares against its reference product. Ultimately, both the healthcare provider and patient want to be comfortable in the knowledge that a biosimilar will produce the same outcomes as the current batches of the reference product.

COST

A key consideration in the use of biologics is the relatively high cost of therapy, which is owing in part to the complexity of drug development and manufacturing processes.[7] For example, patients with moderate to severe psoriasis were more likely to require an inpatient admission or emergency department visit, and to incur medical costs that were, on average, $18,960 greater than controls without the disease.[61] With an estimated prevalence of 7.4 million people in the United States, the total burden of psoriasis may exceed $35 billion, including approximately $12 billion in medical costs, $12 billion from reduced quality of life and $11 billion from productivity losses.[62]

Limited healthcare budgets often restrict access to biologics for many patients, and this remains a hurdle in the United States and elsewhere in the world.[48] Since the inception of the Biologics Price Competition and Innovation Act, interest has grown in the development of biosimilars.[8] This increased competition resulting from biosimilars is expected to drive down prices.[63] Based on estimates from the US National Health and Wellness survey of patients with moderate to severe psoriasis who were commercially insured, approximately 20% received a biologic therapy, suggesting underuse of these agents in this population.[64] Although multiple factors likely account for this, it is conceivable that lower priced biosimilars may increase access to biologic therapy for these individuals. The cost reduction is partly owing to lower research costs, but unlike generic drugs that are up to 90% less expensive than their originator or reference drugs,[65] the projected relative price reduction for biosimilars versus their reference products in the United States is considerably smaller, at an estimated 15-35%.[66]

CONCLUSIONS

Biologics have revolutionized the treatment of immune-mediated chronic diseases, but have placed a growing financial burden on patients and healthcare systems. Just as generics of small-molecule drugs have helped to address costs and patient access to treatment, there are opportunities for biosimilars to provide benefits to the healthcare systems in the United States. At a minimum, biosimilars will compete with their reference products based on quality, price and manufacturer reputation.[67] Following the example set by the EMA, the FDA has defined a streamlined pathway for the approval of biosimilars. Although the regulatory environment for biosimilars will continue to evolve, the licensing of biosimilars has already commenced in the United States. Healthcare providers need to be aware of issues relating to interchangeability at the state level, and access to unbiased information is necessary to make informed and appropriate treatment choices for patients.[12]

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REFERENCES

1. **Jacobs P, Bissonnette R, Guenther LC.** Socioeconomic burden of immune-mediated inflammatory diseases: focusing on work productivity and disability. J Rheumatol Suppl 2011;88:55–61.
2. **Curtis JR, Singh JA.** Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther 2011;33:679–707.
3. **Lloyd S, Bujkiewicz S, Wailoo AJ, et al.** The effectiveness of anti-TNF-alpha therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology (Oxford) 2010;49:2313–21.
4. **Kim IH, West CE, Kwatra SG, et al.** Comparative efficacy of biologics in psoriasis: a review. Am J Clin Dermatol 2012;13:365–74.
5. **Reinisch W, Sandborn WJ, Panaccione R, et al.** 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis 2013;19:1700–9.
6. **Panaccione R, Colombel JF, Sandborn WJ, et al.** Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. Aliment Pharmacol Ther 2013;38:1236–47.
7. **Isaacs JD, Cutolo M, Keystone EC, et al.** Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody. J Intern Med 2016;279:41–59.
8. **Lie G, Sciascia S, Cuadrado MJ.** Biosimilar vs biological agents in rheumatology: when are biosimilar agents similar enough? Int Immunopharmacol 2015;27:220–3.
9. **Papachristou GI, Plevy S.** Novel biologics in inflammatory bowel disease. Gastroenterol Clin North Am 2004;33:251–69, ix.
10. **Kuek A, Hazleman BL, Ostör AJ.** Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J 2007;83:251–60.
11. **Finckh A.** Comparative effectiveness of biologic antirheumatic therapies in rheumatoid arthritis after failure to respond to a first TNF inhibitor. J Comp Eff Res 2012;1:481–4.
12. **Weise M, Bielsky MC, De Smet K, et al.** Biosimilars: what clinicians should know. Blood 2012;120:5111–7.
13. **Beck A, Reichert JM.** Approval of the first biosimilar antibodies in Europe: a major landmark for the biopharmaceutical industry. MAbs 2013;5:621–3.
14. **Alten R, Cronstein BN.** Clinical trial development for biosimilars. Semin Arthritis Rheum 2015;44:S2–8.
15. **Paradise J.** The legal and regulatory status of biosimilars: how product naming and state substitution laws may impact the United States health-care system. Am J Law Med 2015;41:49–84.
16. **Sandoz Inc.** ZARXIO™ (filgrastim-sndz) injection, for subcutaneous or intravenous use. Prescribing information. 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125553s001lbl.pdf. Accessed September 27, 2016.
17. **Pfizer Inc.** INFLECTRA™ (infliximab-dyyb) for Injection, for Intravenous Use. Prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125544s000lbl.pdf; April 2016. Accessed September 20, 2016.
18. **Samsung Bioepis.** RENFLEXIS (infliximab-abda) for Injection, for Intravenous Use. Prescribing information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761054lbl.pdf. Accessed September 1, 2017.
19. **Sandoz Inc.** ERELZI™ (etanercept-szzs) injection, for subcutaneous use. Prescribing information. 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761042lbl.pdf. Accessed October 6, 2016.
20. **Amgen Inc.** AMJEVITA™ (adalimumab-atto) injection for subcutaneous use. Prescribing information. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761024lbl.pdf. Accessed September 27, 2016.
21. **Boehringer Ingelheim Pharmaceuticals, Inc.** CYLTEZO™ (adalimumab-adbm) injection, for subcutaneous use. Prescribing information. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761058lbl.pdf. Accessed September 1, 2017.
22. **Amgen Inc.** MVASI (bevacizumab-awwb) Solution for intravenous infusion. Prescribing information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761028s000lbl.pdf. Accessed October 1, 2017.
23. **Patent Docs.** HUMIRA® Biosimilar update—settlement in AbbVie v. Amgen case announced and AbbVie v. Boehringer Ingelheim litigation begins. 2017. Available at: http://www.patentdocs.org/followon_biologics/. Accessed November 17, 2017.
24. **Boehringer Ingelheim Pharmaceuticals, Inc.** Boehringer Ingelheim Pharmaceuticals, Inc. receives FDA approval for Cyltezo™ (adalimumab-adbm), a biosimilar to Humira®, for the treatment of multiple chronic inflammatory diseases. 2017. Available at: https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-pharmaceuticals-inc-receives-fda-approval-cyltezo-adalimumab. Accessed September 24, 2017
25. **GaBI online.** FDA approves bevacizumab biosimilar Mvasi. 2017. Available at: http://www.gabionline.net/Biosimilars/News/FDA-approves-bevacizumab-biosimilar-Mvasi. Accessed November 17, 2017.
26. **Mellstedt H.** Clinical considerations for biosimilar antibodies. Eur J Cancer Suppl 2013;11:1–11.
27. **Bui LA, Hurst S, Finch GL, et al.** Key considerations in the preclinical development of biosimilars. Drug Discov Today 2015;20(Suppl 1):3–15.
28. **Daubenfeld T, Dassow J, Kessler M, et al.** Understanding the market dynamics of biosimilars. J Business Chemistry 2016;13:33–46.
29. **US Food and Drug Administration.** The drug development process. 2016. http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm. Accessed October 12, 2016.
30. **US Food and Drug Administration.** Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. April 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed December 31, 2015.
31. **Griffith N, McBride A, Stevenson JG, et al.** Formulary selection criteria for biosimilars: considerations for US health-system pharmacists. Hosp Pharm 2014;49:813–25.
32. **Wish JB.** The approval process for biosimilar erythropoiesis-stimulating agents. Clin J Am Soc Nephrol 2014;9:1645–51.
33. **Müller-Ladner U, Hong S, Oh C, et al.** Scientific rationale behind the development and approval of biosimilar infliximab (CT-P13) in Europe. Expert Rev Clin Immunol 2015;11(Suppl 1):S5–14.
34. **Bagel J.** Weighing the prospects of biosimilars. Pract Dermatol 2013;November 46-47.
35. **Blauvelt A, Cohen AD, Puig L, et al.** Biosimilars for psoriasis: preclinical analytical assessment to determine similarity. Br J Dermatol 2016;174:282–6.
36. **Schneider CK.** Biosimilars in rheumatology: the wind of change. Ann Rheum Dis 2013;72:315–8.
37. **Tebbey PW, Varga A, Naill M, et al.** Consistency of quality attributes for the glycosylated monoclonal antibody Humira® (adalimumab). MAbs 2015;7:805–11.
38. **Mehr SR, Zimmerman MP.** Is a biologic produced 15 years ago a biosimilar of itself today?. Am Health Drug Benefits 2016;9:515–8.
39. **Schiestl M, Stangler T, Torella C, et al.** Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol 2011;29:310–2.

40. **US Food and Drug Administration.** Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product: guidance for industry. 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformatin/Guidances/UCM291134.pdf. Accessed December 15, 2015.
41. **Berkowitz SA, Engen JR, Mazzeo JR, et al.** Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov 2012;11:527–40.
42. **Kalman-Szekeres Z, Olajos M, Ganzler K.** Analytical aspects of biosimilarity issues of protein drugs. J Pharm Biomed Anal 2012;69:185–95.
43. **Declerck PJ, Darendeliler F, Goth M, et al.** Biosimilars: controversies as illustrated by rhGH. Curr Med Res Opin 2010;26:1219–29.
44. **Reinisch W, Smolen J.** Biosimilar safety factors in clinical practice. Semin Arthritis Rheum 2015;44:S9–15.
45. **Schellekens H, Lietzan E, Faccin F, et al.** Biosimilar monoclonal antibodies: the scientific basis for extrapolation. Expert Opin Biol Ther 2015;15:1633–46.
46. **Feagan BG, Choquette D, Ghosh S, et al.** The challenge of indication extrapolation for infliximab biosimilars. Biologicals 2014;42:177–83.
47. **US Food and Drug Administration.** FDA News Release. FDA approves Inflectra, a biosimilar to Remicade. 2016. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm. Accessed September 30, 2016.
48. **McCamish M, Woollett G.** Worldwide experience with biosimilar development. MAbs 2011;3:209–17.
49. **Calvo B, Zuñiga L.** The US approach to biosimilars: the long-awaited FDA approval pathway. BioDrugs 2012;26:357–61.
50. **US Food and Drug Administration.** Considerations in demonstrating interchangeability with a reference product: guidance for industry. 2017. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135. Accessed February 9, 2017.
51. **National Conference of State Legislatures.** State laws and legislation related to biologic medications and substitution of biosimilars. 2016. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Accessed September 27, 2016.
52. **Casadevall N, Felix T, Strober BE, et al.** Similar names for similar biologics. BioDrugs 2014;28:439–44.
53. **Fiorino G, Danese S.** The biosimilar road in inflammatory bowel disease: the right way? Best Pract Res Clin Gastroenterol 2014;28:465–71.
54. **Carrascosa JM, van Doorn MB, Lahfa M, et al.** Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. J Eur Acad Dermatol Venereol 2014;28:1424–30.
55. **Dorner T, Kay J.** Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol 2015;11:713–24.
56. **Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, et al.** Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis 2016;75:1693–6.
57. **Teva Pharmaceuticals USA Inc.** GRANIX® (tbo-filgrastim) injection, for subcutaneous use. Prescribing information. 2017. http://granixhcp.com/Pdf/prescribing-information.pdf; Accessed February 8, 2017.
58. **Regeneron Pharmaceuticals Inc.** ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion. Prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125418s039lbl.pdf; Accessed January 24, 2017.
59. **US Food and Drug Administration.** Nonproprietary naming of biological products: guidance for industry. 2017. www.fda.gov/downloads/drugs/guidances/ucm459987.pdf. Accessed January 24, 2017.
60. "Biosimilars": towards fewer obstacles to their use. Prescrire Int 2015;24:80–1,83.
61. **Feldman SR, Zhao Y, Shi L, et al.** Economic and comorbidity burden among patients with moderate-to-severe psoriasis. J Manag Care Spec Pharm 2015;21:874–88.
62. **Vanderpuye-Orgle J, Zhao Y, Lu J, et al.** Evaluating the economic burden of psoriasis in the United States. J Am Acad Dermatol 2015;72:961–7 e5.
63. **Lavalle-González FJ, Khatami H.** The biosimilar insulin landscape: current developments. Postgrad Med 2014;126:81–92.
64. **Armstrong AW, Koning JW, Rowse S, et al.** Under-treatment of patients with moderate to severe psoriasis in the United States: analysis of medication usage with health plan data. Dermatol Ther (Heidelb) 2017;7:97–109.
65. **Dunne S, Shannon B, Dunne C, et al.** A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol 2013;14:1.
66. **Yu B.** Greater potential cost savings with biosimilar use. Am J Manag Care 2016;22:378.
67. **Grabowski HG, Guha R, Salgado M.** Regulatory and cost barriers are likely to limit biosimilar development and expected savings in the near future. Health Aff (Millwood) 2014;33:1048–57.
68. **Declerck PJ.** Biologicals and biosimilars: a review of the science and its implications. GaBi J 2012;1:13–6.
69. **US Food and Drug Administration**. Information for healthcare professionals (biosimiliars). http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm. February 2016. Accessed April 29, 2016.
70. **Rak Tkaczuk KH, Jacobs IA.** Biosimilars in oncology: from development to clinical practice. Semin Oncol 2014;41(Suppl 3):S3–12.

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