Potential of Biosimilars to Increase Access to Biologics: Considerations for Advanced Practice Providers in Oncology

SARA M. TINSLEY,[1] PhD, ARNP, AOCN®, CAROLYN GRANDE,[2] CRNP, AOCNP®, KARIN OLSON,[3] PhD, PA-C, LEAH PLATO,[4] PA-C, MPH, CCRP, and IRA JACOBS,[5] MD, JD, MBA, FACS

From [1]Moffitt Cancer Center and University of South Florida, College of Nursing, Tampa, Florida; [2]Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; [3]Eastern Michigan University, Ypsilanti, Michigan; [4]Mary Crowley Cancer Research Center, Dallas, Texas; [5]Pfizer Inc, New York, New York

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Sara Tinsley, 12902 Magnolia Drive, Malignant Hematology, MCB, Tampa, FL 33612. E-mail: sara.tinsley@moffitt.org

https://doi.org/10.6004/jadpro.2018.9.7.2

Abstract

Biosimilars are biologic products that are highly similar, but not identical, to a licensed reference (or "originator") biologic product. These agents have the potential to provide efficiencies and improve access to treatment for patients. Biosimilars are currently available for use in clinical practice, including oncology indications, and several more are in clinical development. Due to several key differences in their fundamental properties, production and manufacturing of biosimilars is more complex compared with that of small-molecule generic drugs. Accordingly, the generic drug approval process is not suitable or transferable to biosimilars, the approval of which involves extensive and thorough comparison with the originator biologic. Advanced practice providers play an important role in evaluating treatment options available to patients, prescribing, patient education, and product monitoring. In order to perform these tasks effectively, advanced practice providers should understand the concepts related to biosimilars in clinical practice, particularly regarding extrapolation to other indications, product labeling, interchangeability between products, and routine pharmacovigilance, among other clinical considerations. However, many health-care providers have limited awareness and minimal experience regarding biosimilars. Thus, the purpose of this review is to provide an overview of biosimilars and discuss the clinical considerations for oncology advanced practice providers concerning these therapies.

Due to their structure, chemically derived drugs such as small molecules can be readily characterized and produced with high purity on a large scale (Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic,

J Adv Pract Oncol 2018;9(7):699–716

2006; Schellekens, 2009). In contrast, biologic drugs are large compounds produced in living organisms, e.g., viruses, bacteria, and eukaryotic cells, through recombinant DNA technology or controlled gene expression (Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann and Covic, 2006; Schellekens, 2009). The first biologic drugs were introduced in the 1980s, and many are proteins that are similar or identical to human proteins, e.g., insulin and growth hormone, or they are monoclonal antibodies targeted to specific proteins within the body (Crommelin et al., 2005; Dombrowski, 2013). Due to the structural complexity of biologic drugs, small modifications to the compound or surrounding environment during the manufacturing process, storage, or handling can greatly impact their safety and efficacy (Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann and Covic, 2006).

Over 80% of the US biologic therapy revenue in 2015 was from biologic therapies used for oncology indications, and revenue is expected to grow due to the rising incidence of cancer and increased utilization of biologic medicines within the clinic (Global Market Insights, 2016). This trend is not restricted to the United States, and the global biologic therapy market for oncology is expected to reach $100 billion by 2023 (Global Market Insights, 2016).

Biologic drugs are mainstay therapies in the treatment of several diseases, such as cancer, rheumatoid arthritis, and inflammatory bowel disease. Examples of biologics for oncology indications include antineoplastic monoclonal antibodies such as rituximab (Rituxan, also known as MabThera outside the United States), bevacizumab (Avastin), and trastuzumab (Herceptin); and hematopoietic growth factors such as epoetin (Epogen, Procrit) and filgrastim (Neupogen; National Cancer Institute, 2016). Despite biologic medicines revolutionizing the treatment of cancer and chronic diseases, access to these agents can be restricted, e.g., due to availability, insurance coverage, and/or cost (Baer et al., 2014; Lammers et al., 2014; Monk, Lammers, Cartwright, & Jacobs, 2017; Socinski et al., 2015). However, patents and marketing exclusivity for many biologics have expired or will expire in the next several years (Philippidis, 2014). These factors provide impetus for the development of biosimilars.

In terms of clinical relevance, biosimilars are distinct from generic drugs and they cannot be considered generic equivalents of biologic drugs (Declerck, Danesi, Petersel, & Jacobs, 2017). Generic drugs are identical copies of their original drugs, whereas biosimilars are biologic products that are highly similar, but not identical, to a licensed reference biologic (or "originator") product, such that there are "no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency," notwithstanding minor differences in inactive components (US Food and Drug Administration, 2015b).

High-quality biosimilars that are safe and efficacious could potentially increase access to biologic treatments, leading to improvements in clinical outcomes for patients and health-care system efficiencies (Bennett et al., 2014; McCamish and Woollett, 2012). Indeed, biosimilars are now available in many countries, including the United States, and their introduction has been linked with both increased patient access and cost savings (IMS Institute for Healthcare Informatics, 2016a). Due to the potential impact of biosimilars, oncology advanced practice providers must be well-equipped with knowledge regarding these therapies.

In the United States, advanced practice providers now constitute 22% of the health-care provider workforce (IMS Institute for Healthcare Informatics, 2016b). As of 2015, 17% of all retail prescriptions (676 million prescriptions) were written by advanced practice providers, which is a substantial increase from 9% of all retail prescriptions (327 million prescriptions) in 2010 (IMS Institute for Healthcare Informatics, 2016b). However, many health-care providers have limited awareness and minimal experience regarding biosimilars (Cohen et al., 2017; Hemmington et al., 2017; Mayden, Larson, Geiger, & Watson, 2015; Molinari et al., 2016; Pasina, Casadei, & Nobili, 2016; Rak Tkaczuk & Jacobs, 2014). Therefore, as the use of biosimilars becomes more widespread, advanced practice providers should understand the development process for these agents and the role of biosimilars in increasing treatment options for patients. This review provides an overview of biosimilars and discusses the clinical considerations for oncology advanced practice providers.

DEVELOPMENT AND MANUFACTURING PROCESS OF BIOSIMILARS

To understand why biosimilars are distinct from generic drugs, it is helpful to first consider how biologic products and small-molecule, chemically derived drugs differ with respect to their fundamental properties and manufacturing processes (Figure 1). In terms of structure and size, small-molecule drugs are simple structures with low molecular weight, whereas biologic products have high molecular weight and complex structures and, on average, are 100- to 1,000-fold larger than small-molecule drugs (Berkowitz, Engen, Mazzeo, & Jones, 2012; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006; Schellekens, 2009).

In terms of manufacturing and production, small-molecule drugs are produced using chemical synthesis with recognized, easily obtained reagents. In comparison, the development of biologic products is significantly more complex, involving multiple stages, each with the potential to impact the final product (Figure 2; Berkowitz et al., 2012; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006). First, the relevant protein sequence is cloned, inserted into a vector, and transfected into a host cell; the host cell can be bacterial or eukaryotic. Next, through cell screening and selection, a master cell line is established; this master cell line should express the recombinant protein in sufficient amounts and with the necessary posttranslational modifications. Additional cells are then cultured in substantial quantities using optimal growth conditions, followed by large-scale protein purification steps. Thereafter, the three-dimensional structure, uniformity, heterogeneity, and potency of the protein product is examined using a variety of sensitive analytical techniques, as well as functional bioassays. Finally, the formulated biologic drug is packaged, stored, and distributed under optimal environmental conditions to ensure the integrity and stability of the product (Berkowitz et al., 2012; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006).

The protein structure of biologic products can be affected by a variety of factors, including, but not limited to, alterations to the primary amino acid sequence, oligomerization, glycosylation, protein folding, and environmental factors such as temperature and moisture (Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006). Consequently, the safety and effectiveness of the biologic product can be affected by alterations in the manufacturing process; for example, changes to the expression system (e.g., use of a different vector), modifications to the culture conditions or purification methods (e.g., changing growth media, reagents, or operating methods for optimization or economic reasons), upscaling of the process for large-scale manufacturing of the product, or modulation of storage and packaging conditions (e.g., using different stabilizers, buffers, or environmental factors; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006).

Many of these factors have the potential to influence the immunogenicity of biologic products. Immunogenicity is the ability of a substance to elicit an immune response. There may be no clinical consequence for developing an immune response to a biologic product. However, for biologic products, including biosimilars, the presence of antibodies can sometimes be associated with immune-related adverse events, reduced or increased efficacy, or neutralization of the endogenous protein (Camacho, Frost, Abella, Morrow, & Whittaker, 2014; Crommelin et al., 2005; Schellekens, 2009; Singh, 2011; Socinski et al., 2015). Therefore, biologic products are more sensitive to changes in manufacturing, storage, and handling conditions, and have a higher immunogenic potential, compared with small-molecule drugs (Camacho et al., 2014; Crommelin et al., 2005; Schellekens, 2009; Singh, 2011; Socinski et al., 2015).

Due to the comparative ease of production, it is possible for manufacturers of small-molecule drugs to produce generic versions that contain an identical active ingredient to that of the corresponding originator product. These can be produced in large quantities and with high purity and stability. In contrast, and due to the complexities and proprietary nature of manufacturing conditions, it is likely not possible for the originator biologic product to be duplicated precisely, and some heterogeneity will almost certainly exist between the biosimilar and the reference product

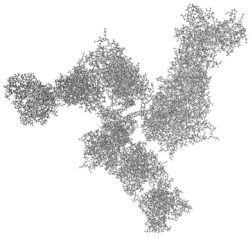
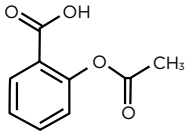
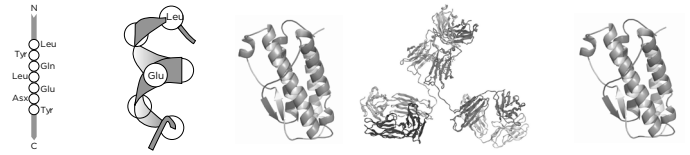
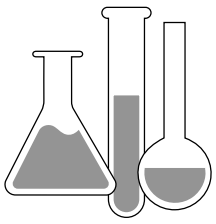
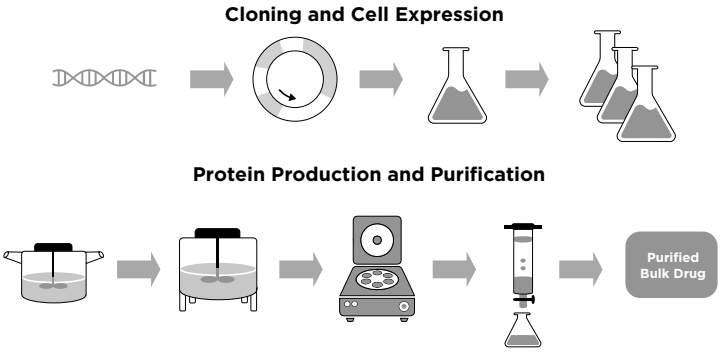
Characteristic	Small-molecule generic drug	Biosimilar
Structure and size	• Simple structure with a low molecular weight 	• Complex structure with a large molecular weight 
Characterization and analysis	• Straightforward to analyze and characterize • Readily available analytical tool 	• Full characterization is difficult due to structural complexity • Analytical tools are limited and a greater level of sensitivity is required 
Manufacturing process	• Chemical synthesis • Easily duplicated • Reagents readily available 	• Complex, multistage process involving cloning of relevant protein of interest, transfection into host cells, cell screening, and selection, and lastly, large-scale protein expression and purification • Cannot be precisely duplicated • Changes to any stage of the process (e.g., expression system or growth conditions) can have a substantial impact on final product  (See Figure 2)
Purity and stability	• High level of purity and stability	• Heterogeneous • Sensitive to changes in manufacturing process, environmental factors, storage, and handling
Regulatory approval	• Demonstration of bioequivalence using analytical testing and comparative bioavailability studies	• Extensive and thorough comparison with the originator involving several types of studies (in vitro analytical studies, nonclinical animal studies and a tailored clinical trial program) performed in a stepwise manner

Figure 1. Summary of the major differences between biosimilars and generics in terms of fundamental properties, development, and regulation. PTM = posttranslational modification. Information from Berkowitz et al. (2012); Crommelin et al. (2005); Daller (2016); Dombrowski (2013); Kuhlmann & Covic (2006); Schellekens (2009).

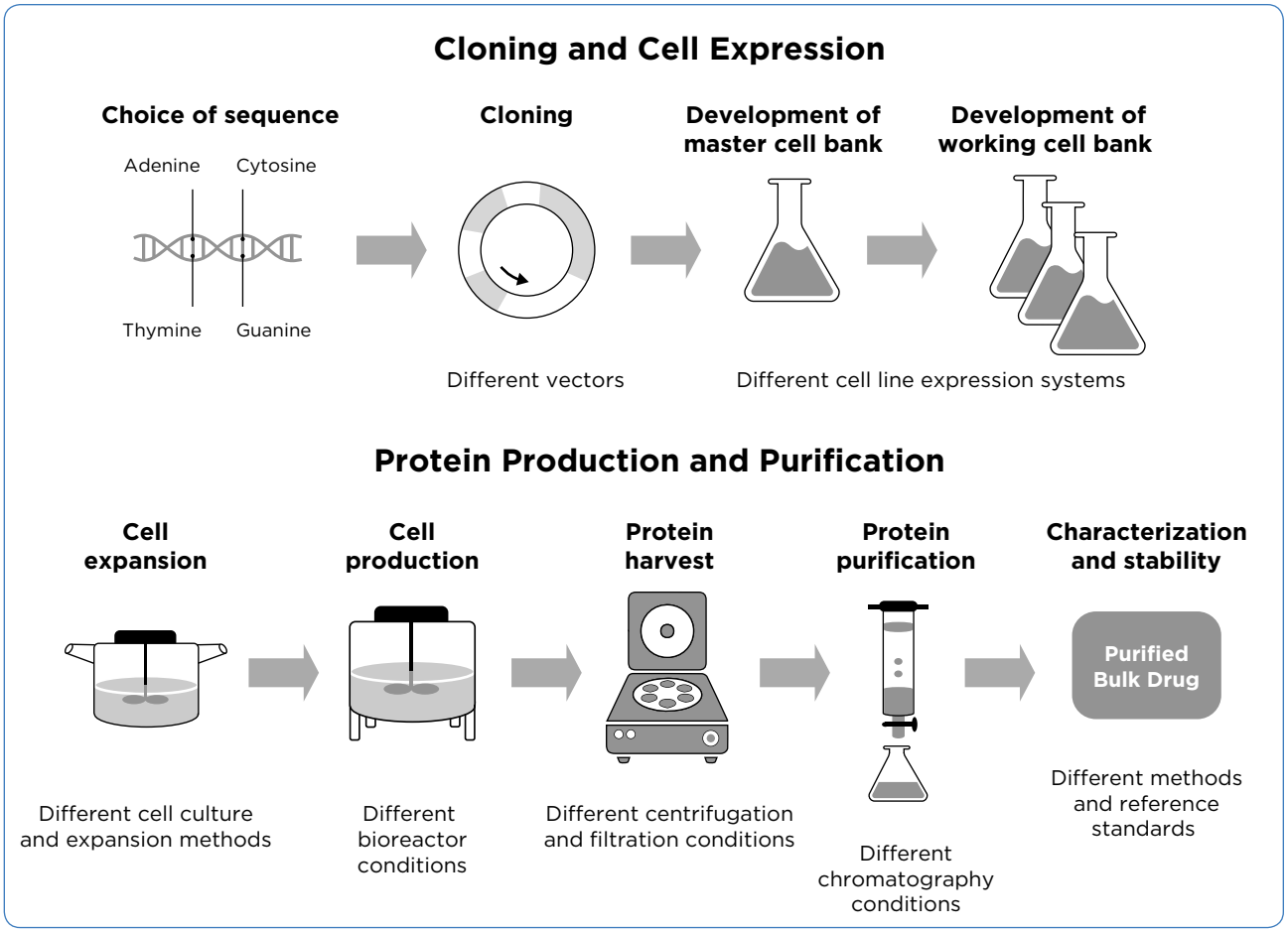


Figure 2. Development process for biosimilars. Information from Berkowitz et al. (2012); Crommelin et al. (2005); Daller (2016); Dombrowski (2013); Kuhlmann & Covic (2006).

(Berkowitz et al., 2012; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006; Schellekens, 2009). Furthermore, prior to biosimilar development, the originator product must be fully characterized in terms of its structural, physicochemical, and biologic properties. Due to the larger size and greater complexity of the reference biologic product, it is more challenging to achieve this compared with development of a small-molecule generic drug. Several layers of protein structure, from the primary amino acid sequence through to the higher-order folding of the protein, as well as posttranslational modifications, must be fully understood and characterized, as any modifications could introduce variability in terms of structure, function, purity, and immunogenicity (Berkowitz et al., 2012; Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Kuhlmann & Covic, 2006).

REGULATORY APPROVAL PROCESS FOR BIOSIMILARS

For small-molecule generic drugs, approval is obtained on the basis of demonstrating bioequivalence to the corresponding originator product using analytical testing and comparative bioavailability studies. Nonclinical (animal) and clinical studies are generally not required (US Food and Drug Administration, 2016a). The small-molecule generic drug approval process is not suitable for or transferrable to biosimilars, which involves a more extensive and rigorous comparison with the originator (Weise et al., 2011). The purpose is to establish a high degree of similarity to the originator rather than to demonstrate clinical safety and efficacy, which have already been established for the reference product (Weise et al., 2012). Any heterogeneity between the biosimilar and the originator is evaluated to ensure there are no meaningful dif-

ferences in terms of physicochemical and biologic characteristics, efficacy, safety, immunogenicity, and purity.

Although some differences exist, regulatory requirements for the approval of biosimilars are generally consistent across the major regulatory guidelines, e.g., European Medicines Agency (EMA; European Medicines Agency, 2014), the US Food and Drug Administration (FDA; US Food and Drug Administration, 2015b), and World Health Organization (WHO; World Health Organization, 2009), as well as guidelines in other highly regulated markets, such as Canada and Japan (Health Canada, 2016; Ministry of Health Labour and Welfare, 2013). Biosimilar or biosimilarity as defined in the FDA guidelines means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (US Food and Drug Administration, 2015b).

To demonstrate biosimilarity, several types of studies, performed in a stepwise manner, are required (Figure 3; European Medicines Agency, 2014; US Food and Drug Administration, 2015b; World Health Organization, 2009). First, in vitro analytical studies are performed in order to demonstrate that the biosimilar is highly similar to the reference product in terms of structure (e.g., the same amino acid sequence), higher-order structure and posttranslational modifications, and function (e.g., similar response observed during target/receptor-binding or cell-based assays). If the biosimilar is a monoclonal antibody, additional assessments of antibody-dependent, cell-mediated cytotoxicity and complement-depen-

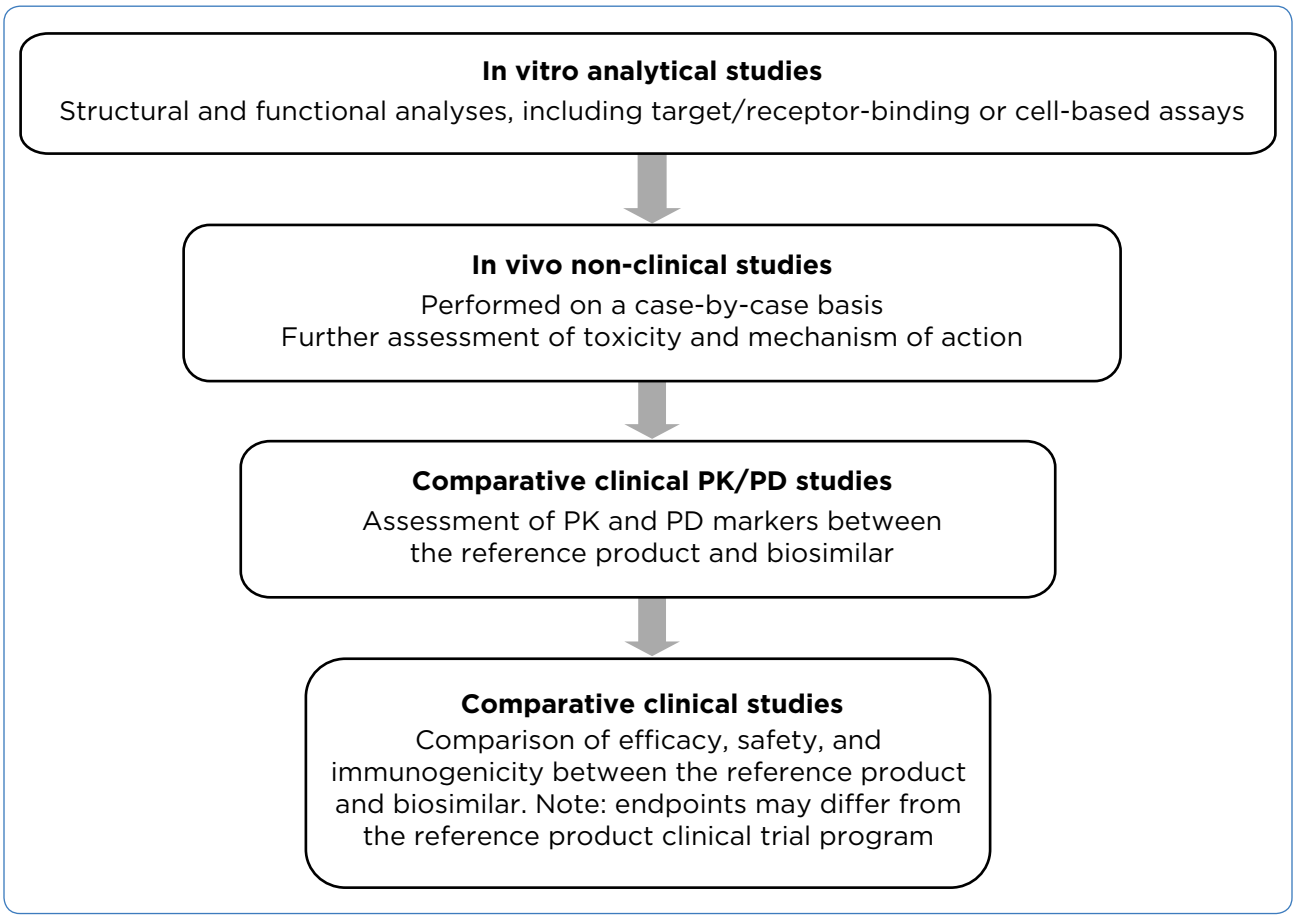


Figure 3. Regulatory process for biosimilars. PD = pharmacodynamics; PK = pharmacokinetics. Information from European Medicines Agency (2014); US Food and Drug Administration (2015b); World Health Organization (2009).

dent cytotoxicity are generally required. The results from the structural and functional analyses form a much larger part of the regulatory approval application for biosimilars compared with reference biologic products (Berkowitz et al., 2012). Next, if necessary, the analytical studies are followed by nonclinical animal studies to establish that the biosimilar has the same clinically relevant mechanism of action and functional activity, as well as similar toxicity, as the originator product. Finally, a tailored, comparative clinical trial program is performed to compare the pharmacokinetics, pharmacodynamics, clinical efficacy, clinical safety, and immunogenicity of the biosimilar to the reference product. The purpose of this program is to establish similarity between the two products, and it is not to duplicate the clinical trial program of the originator. The type of animal and clinical studies required for approval are dependent on several factors, such as the reference product and the preceding analytical data (European Medicines Agency, 2014; Socinski et al., 2015; US Food and Drug Administration, 2015b; World Health Organization, 2009).

Usually, a biosimilar's clinical trial program consists of two stages. First, pharmacokinetics and pharmacodynamics are assessed in a head-to-head clinical study, and this generally involves healthy volunteers. This is followed by an evaluation of efficacy, safety, and immunogenicity across one or more comparative trials in patients. Since the focus of the clinical trial program is to demonstrate biosimilarity, the trial design, sample size, and endpoints may differ from those of the reference product, and should address any remaining concerns surrounding product-related differences in efficacy and safety between the biosimilar and originator product (Socinski et al., 2015).

The stepwise approach to establishing biosimilarity should demonstrate that any heterogeneity between the biosimilar and the originator product as a result of the biosimilar's unique manufacturing process does not result in significant alterations in structural and functional characteristics, or clinical pharmacology, efficacy, safety, or immunogenicity (European Medicines Agency, 2014; Socinski et al., 2015; US Food and Drug Administration, 2015b; World Health Organization, 2009).

The data from all stages of development are important for regulatory approval and medical acceptance. Biosimilar approval is granted based on "totality of the evidence" (US Food and Drug Administration, 2015b). Although the provision of an extensive data package is required for biosimilar approval, the demonstration of a high degree of similarity between the biosimilar and reference product in analytical assessments provides the rationale for a reduced nonclinical and clinical dataset compared with that required for licensing an originator biologic product (World Health Organization, 2009). Finally, it is important to note that although overall guidelines exist, biosimilar approvals are made on an individual case-by-case basis, and the developers of a biosimilar product work with regulatory agencies to establish the relevant analytical, nonclinical, and clinical studies required to support approval (European Medicines Agency, 2014; US Food and Drug Administration, 2015b; World Health Organization, 2009).

CURRENT STATUS OF BIOSIMILARS IN THE CLINIC

As of November 2, 2018, 49 biosimilars are authorized in Europe, and 14 biosimilars are currently licensed in the United States. Additional biosimilar applications are under evaluation by the EMA and FDA, with many more in development. The first monoclonal antibody biosimilars were recently approved by the EMA, FDA, and regulatory agencies in other countries for the treatment of inflammatory diseases (e.g., rheumatoid arthritis and inflammatory bowel disease). These include biosimilars of infliximab (Remicade) and adalimumab (Humira; Biogen, 2016; European Medicines Agency, 2013, 2017b; Generics and Biosimilars Initiative [GaBI] Online, 2012, 2014; US Food and Drug Administration, 2016b, 2016d).

Epoetin, filgrastim, and pegfilgrastim biosimilars are available for use in supportive care in various regions worldwide (Table 1). In Europe, there are currently five epoetin, seven filgrastim, two pegfilgrastim, one bevacizumab, and four trastuzumab biosimilars authorized for use in patients with cancer, as well as six rituximab biosimilars for patients with blood cancers and inflammatory conditions. The filgrastim biosimilar, Zarxio, was the first biosimilar to be licensed by the FDA in 2015 for sup-

Table 1. Biosimilars Available for Use in Oncology Indications in Europe and the United States

Reference product	Biosimilar	Manufacturer	Date of licensing / authorization	Oncology indication
Europe				
Rituximab (MabThera)	Blitzima	Celltrion Healthcare Hungary Kft	July 13, 2017	• Treatment of adults with the following blood cancers and inflammatory conditions: » Follicular lymphoma and diffuse large B-cell non-Hodgkin lymphoma » Chronic lymphocytic leukemia » Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis
	Ritemvia	Celltrion Healthcare Hungary Kft	July 13, 2017	
	Rituzena	Celltrion Healthcare Hungary Kft	July 13, 2017	
	Rixathon	Sandoz GmbH	June 15, 2017	
	Riximyo	Sandoz GmbH	June 15, 2017	
	Truxima	Celltrion Healthcare Hungary Kft	February 17, 2017	
Epoetin (Eprex/ Erypo)	Retacrit	Hospira UK Ltd	December 18, 2007	• Treatment of anemia in adult patients receiving chemotherapy for solid tumors, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g., cardiovascular status, preexisting anemia at the start of chemotherapy)
	Silapo	Stada Arzneimittel AG	December 18, 2007	
	Abseamed	Medice Arzneimittel Pütter GmbH & Co. KG	August 28, 2007	
	Binocrit	Sandoz GmbH	August 28, 2007	
	Epoetin Alfa Hexal	Hexal AG	August 28, 2007	
Filgrastim (Neupogen)	Accofil	Accord Healthcare Ltd	September 18, 2014	• Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) • Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia
	Grastofil	Apotex Europe BV	October 18, 2013	
	Nivestim	Hospira UK Ltd	June 8, 2010	
	Filgrastim Hexal	Hexal AG	February 6, 2009	
	Zarzio	Sandoz GmbH	February 6, 2009	
	Ratiograstim	Ratiopharm GmbH	September 15, 2008	
	Tevagrastim	Teva GmbH	September 15, 2008	
Pegfilgrastim (Neulasta)	Pelgraz	Accord Healthcare Ltd	September 21, 2018	• Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes)
	Udenyca	ERA Consulting GmbH	September 20, 2018	
Trastuzumab (Herceptin)	Trazimera	Pfizer Europe MA EEIG	July 26, 2018	• Treatment of adult patients with HER2-positive metastatic breast cancer • Treatment of adult patients with HER2-positive early breast cancer • Treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anticancer treatment for their metastatic disease
	Kanjinti	Amgen Europe BV, Breda	May 16, 2018	
	Herzuma	Celltrion Healthcare Hungary Kft	February 9, 2018	
	Ontruzant	Samsung Bioepis UK Ltd	November 15, 2017	

Note. Information correct as of November 2, 2018. EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor. Information from European Medicines Agency (2018b); US Food and Drug Administration (2018).

Table 1. Biosimilars Available for Use in Oncology Indications in Europe and the United States (cont.)

Reference product	Biosimilar	Manufacturer	Date of licensing / authorization	Oncology indication
Europe (cont.)				
Bevacizumab (Avastin)	Mvasi	Amgen Europe BV	January 15, 2018	• In combination with fluoropyrimidine-based chemotherapy for treatment of adult patients with metastatic carcinoma of the colon or rectum • In combination with paclitaxel, as first-line treatment of adult patients with metastatic breast cancer • In addition to platinum-based chemotherapy, as first-line treatment of adult patients with unresectable advanced, metastatic, or recurrent non–small cell lung cancer other than predominantly squamous cell histology • In combination with erlotinib, as first-line treatment of adult patients with unresectable advanced, metastatic or recurrent nonsquamous non–small cell lung cancer with *EGFR* activating mutations • In combination with interferon alfa-2a, as first-line treatment of adult patients with advanced and/or metastatic renal cell cancer • In combination with carboplatin and paclitaxel, as front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer • In combination with carboplatin and gemcitabine or with carboplatin and paclitaxel, for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents • In combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin, for treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan in patients who cannot receive platinum therapy, for treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix

Note. Information correct as of November 2, 2018. EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor. Information from European Medicines Agency (2018b); US Food and Drug Administration (2018).

☞ *Table continued on next page*

Table 1. Biosimilars Available for Use in Oncology Indications in Europe and the United States (cont.)

Reference product	Biosimilar	Manufacturer	Date of licensing / authorization	Oncology indication
United States				
Filgrastim (Neupogen)	Filgrastim-aafi (Nivestym)	Hospira Inc, a Pfizer Company	July 20, 2018	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia • Reduce the duration of neutropenia and neutropeniarelated clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
	Filgrastim-sndz (Zarxio)	Sandoz Inc	March 6, 2015	
Pegfilgrastim (Neulasta)	Pegfilgrastim-cbqv (Udenyca)	Coherus BioSciences Inc	November 2, 2018	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia
	Pegfilgrastim-jmdb (Fulphila)	Mylan GmbH	June 4, 2018	
Bevacizumab (Avastin)	Bevacizumab-awwb (Mvasi)	Amgen Inc	September 14, 2017	• Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. Mvasi is not indicated for the adjuvant treatment of surgically resected colorectal cancer • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for the second-line treatment of patients who have progressed on a first-line bevacizumab product-containing regimen • Nonsquamous non–small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease • Glioblastoma with progressive disease following prior therapy, based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with bevacizumab products • Metastatic renal cell carcinoma, in combination with interferon alfa • Cervical cancer that is persistent, recurrent, or metastatic disease, in combination with paclitaxel and cisplatin or paclitaxel and topotecan

Note. Information correct as of November 2, 2018. EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor. Information from European Medicines Agency (2018b); US Food and Drug Administration (2018).

Table 1. Biosimilars Available for Use in Oncology Indications in Europe and the United States (cont.)

Reference product	Biosimilar	Manufacturer	Date of licensing / authorization	Oncology indication
United States (cont.)				
Trastuzumab (Herceptin)	Trastuzumab-dkst (Ogivri)	Mylan GmbH	December 1, 2017	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Epoetin alfa (Epogen/ Procrit)	Epoetin alfa-epbx (Retacrit)	Hospira Inc, a Pfizer Company	May 15, 2018	• Treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy

Note. Information correct as of November 2, 2018. EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor. Information from European Medicines Agency (2018b); US Food and Drug Administration (2018).

portive care in oncology (US Food and Drug Administration, 2015a). The bevacizumab biosimilar, Mvasi, was the first biosimilar licensed for the treatment of adult patients with certain colorectal, lung, brain, kidney, and cervical cancers in the United States (US Food and Drug Administration, 2017b). In the European Union and United States, patents for monoclonal antibodies used in the treatment of cancer have expired or will soon expire (Philippidis, 2014). As a result, more biosimilars for rituximab, trastuzumab, and bevacizumab will likely become available in the near future. Indeed, a number of biosimilars for these monoclonal antibodies are currently undergoing comparative clinical trials (Table 2; Rugo, Linton, Cervi, Rosenberg, & Jacobs, 2016).

CONSIDERATIONS AND IMPLICATIONS FOR ADVANCED PRACTICE PROVIDERS

As more biosimilars obtain regulatory approval and become available for use in clinical practice, advanced practice providers will play an important role in evaluating the treatment options available to patients, as well as understanding any differences between products in prescribing, handling, and/or storage. Furthermore, advanced practice providers will play a critical role in prescribing and providing patient education and awareness regarding biosimilars, in addition to the ongoing assessment and monitoring of biosimilars in the clinic. In order to perform these tasks effectively, clinicians must understand several key considerations regarding biosimilars (Table 3).

Dosing and Route of Administration

In addition to having similar efficacy and safety profiles to their originator products, biosimilars are required to have the same dosing and route of administration as the originator. This should facilitate the transition of biosimilars into the clinic and limit the introduction of different features that may alarm or confuse patients or practitioners (Weise et al., 2012). This is particularly important for any biosimilars that have to be self-administered by the patient, such as filgrastim.

Naming of Biosimilars

The naming of biosimilars is critically important because of its potential impact on the prescribing and dispensing of medicines, and many prescribing advanced practice providers rely on product names to distinguish among different products. Currently, there is no international consensus on the naming of biosimilars, although nomenclature requirements are consistent within each regulatory region (Daller, 2016; European Medicines Agency, 2014; Rugo et al., 2016; Socinski et al., 2015; US Food and Drug Administration, 2017c; Weise et al., 2012; World Health Organization, 2009). In the United States, the FDA guidance is for the biosimilar to bear a nonproprietary name that includes an FDA-designated distinguishing suffix (devoid of meaning and composed of four lowercase letters), e.g., infliximab-dyyb for Inflectra (US Food and Drug Administration, 2017c). As a result of inconsistent naming of biosimilar products across the major regulatory agencies, drug reporting confusion, misattribution of adverse events,

Table 2. Proposed Biosimilar Products in Development for Oncology With Registered Comparative Clinical Trials

Reference product	Biosimilar	Manufacturer	Status	Setting for comparative clinical trial
Bevacizumab (Avastin)	SB8	Samsung Bioepis Co. Ltd	Active, not recruiting	Non–small cell lung cancer
	BCD-021	Biocad	Completed	Non–small cell lung cancer
	PF-06439535	Pfizer Inc	Completed	Non–small cell lung cancer
	CBT124	Cipla BioTec Pvt Ltd	Not yet recruiting	Non–small cell lung cancer
	BI 695502	Boehringer Ingelheim India Pvt Ltd	Active, not recruiting	Non–small cell lung cancer
	FKB238	Centus Biotherapeutics Ltd	Active, not recruiting	Non–small cell lung cancer
	MB02	mAbxience SA	Recruiting	Non–small cell lung cancer
	RPH-001	TRPHARM	Unknown	Non–small cell lung cancer
	MIL60	Beijing Mabworks Biotech Co. Ltd	Recruiting	Non–small cell lung cancer
Pegfilgrastim (Neulasta)	Eurofarma's pegfilgrastim	Eurofarma Laboratorios SA	Withdrawn	Breast cancer
	PLIVA/Mayne filgrastim	Hospira UK Ltd	Completed	Breast cancer
	F-627	Generon (Shanghai) Corporation Ltd	Recruiting	Breast cancer
	LA-EP2006	Sandoz	Completed	Breast cancer
	Lonquex (lipegfilgrastim)	Merckle GmbH	Completed	B-cell non-Hodgkin lymphoma
Rituximab (Rituxan; MabThera)	BCD-020	CJSC BIOCAD Russia	Completed	CD20-positive indolent non-Hodgkin lymphoma
	RTXM83	mAbxience SA	Completed	Diffuse large B-cell lymphoma
	PF-05280586	Pfizer Inc	Completed	CD20-positive low tumor burden follicular lymphoma
	MabionCD20	MABION SA	Recruiting	CD20-positive diffuse large B-cell lymphoma
	ABP 798	Amgen Inc	Recruiting	CD20-positive B-cell non-Hodgkin lymphoma
	SAIT101	Archigen Biotech Ltd	Recruiting	CD20-positive low tumor burden follicular lymphoma
	HLX01	Shanghai Henlius Biotech	Completed	Non-Hodgkin B-cell lymphoma
Trastuzumab (Herceptin)	BCD-022	Biocad	Completed	HER2-positive metastatic breast cancer
	HLX02	Shanghai Henlius Biotech	Recruiting	HER2-positive metastatic breast cancer
	HD201	Prestige Biopharma Pte Ltd	Active, not recruiting	HER2-positive early breast cancer

Note. Studies are registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform, or the European Union Clinical Trials Register. Studies tabulated are those categorized as "phase III" trials in these registries. HER2 = human epidermal growth factor receptor 2. Information correct as of November 2, 2018. Information from European Medicines Agency (2018a); US National Library of Medicine (2018); World Health Organization (2018).

Table 3. Glossary of Terms and Key Points

Term	Definition
Antibody-dependent cytotoxicity	A mechanism of cell-mediated immune defense whereby an effector cell of the immune system actively lyses a target cell whose membrane-surface antigens have been bound by specific antibodies. It is characterized by the release of the content of cytotoxic granules or by the expression of cell death–inducing molecules.
Bioavailability	The fraction of an administered dose of unchanged drug that reaches the systemic circulation. It is a measurement of the rate and extent of a drug at the site of action.
Bioequivalence	Indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues.
Biosimilar	A biologic product that is highly similar, but not identical, to a licensed reference biologic (or "originator") product, such that there are "no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency," notwithstanding minor differences in inactive components.
Biosimilarity	The biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency.
Clinical trial program	For biosimilars, this usually consists of two stages: head-to-head pharmacokinetic and pharmacodynamic studies, followed by evaluation of efficacy, safety, and immunogenicity across one or more comparative trials in patients.
Complement-dependent cytotoxicity	A process of the immune system whereby the membranes of pathogens are damaged without the involvement of antibodies or cells of the immune system, resulting in lysis or cell death.
Extrapolation	The approval of a biosimilar for use in an indication held by the originator but not directly studied in a comparative clinical trial with the biosimilar.
Generic drug	A pharmaceutical drug that is equivalent to a brand-name product in dosage, strength, route of administration, quality, performance, and intended use.
Immunogenicity	The ability of a substance to provoke an immune response. For biologic products, the presence of antibodies can sometimes be associated with immune-related adverse events, reduced or increased efficacy, or neutralization of the endogenous protein.
Interchangeability	The concept that two products can be exchanged for one another without a significant risk of harm to the patient.
Nonclinical data	Designed to detect differences in response between the biosimilar and reference product. Usually consist of in vitro analytical studies to assess structure, higher-order structure, and function. Functional assays include target/receptor-binding or cell-based assays. If the biosimilar is a monoclonal antibody, additional assessments of antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity are generally required. If necessary, the analytical studies are followed by nonclinical animal studies to establish whether the biosimilar has the same clinically relevant mechanism of action and functional activity, as well as similar toxicity, as the originator product.
Nonproprietary name	A short name for a drug that is not subject to trademark (proprietary) rights but is recognized or recommended by government agencies.
Pharmacodynamics	Generally described as what the drug does to the body. It refers to the study of the biochemical, physiologic, and molecular effects of drugs on the body, and involves receptor binding, postreceptor effects, and chemical interactions.
Pharmacokinetics	Generally described as what the body does to the drug. It refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.
Pharmacovigilance	The detection, assessment, and prevention of adverse effects after a product is launched onto the market.

Note. Information from Berkowitz et al. (2012); Camacho et al. (2014); Crommelin et al. (2005); Daller (2016); Declerck et al. (2017); Dombrowski (2013); European Medicines Agency (2017a); Kuhlmann & Covic (2006); Schellekens (2009); Singh (2011); Socinski et al. (2015).

and insufficient monitoring of safety could occur. One approach to assist clinicians with appropriate prescribing and dispensing, as well as adequate safety monitoring, could be to support the use of biosimilar names that are not only distinguishable from their originator products but also reflect the unique manufacturing process and origin of the biosimilar. Efforts are underway to harmonize nomenclature globally, and further developments are awaited.

Product Labeling and Prescribing Information

Consistent policies regarding product labeling and prescribing information do not exist across the regulatory agencies (Daller, 2016; European Medicines Agency, 2012; Rugo et al., 2016; Socinski et al., 2015; US Food and Drug Administration, 2016e; Weise et al., 2012; World Health Organization, 2009). This is a key consideration, as many health-care providers within clinical practice routinely use prescribing information or summaries of product characteristics as an up-to-date point of reference (Dolinar and Reilly, 2014; Hallersten, Fürst, & Mezzasalma, 2016; Rak Tkaczuk and Jacobs, 2014). US Food and Drug Administration guidance states that the biosimilar label must incorporate any relevant data from the originator product labeling, with appropriate product-specific modifications, e.g., information regarding the safe and effective use of the biosimilar or specific storage or handling requirements (US Food and Drug Administration, 2016e). On the other hand, other guidelines (e.g., those from the WHO and EMA) advise that the labeling and prescribing information for biosimilars be as similar as possible, if not identical, to the originator (European Medicines Agency, 2012; World Health Organization, 2009). Consequently, the evidence supporting the approval of the biosimilar (e.g., analytical studies or head-to-head clinical studies) may not be readily available to advanced practice providers, or they may incorrectly assume that the data available for the originator were obtained for the biosimilar. A lack of understanding of these issues may contribute to questions surrounding biosimilar quality, efficacy, and safety, as well as negatively impact the ability of advanced practice providers to present clear information and guidance on biosimilars to patients and other health-care providers. In summary, advanced practice providers need to be aware of the requirements concerning biosimilar labeling and prescribing information in their country, and that they may need to consult the websites of the regulatory bodies to review the evidence used to support biosimilar approval.

Extrapolation

Extrapolation is the use of a biosimilar in an indication held by the reference product, but without comparative trial assessment of the biosimilar in that indication (Daller, 2016; European Medicines Agency, 2014; Rugo et al., 2016; Socinski et al., 2015; US Food and Drug Administration, 2015b; Weise et al., 2012; Weise, Kurki, Wolff-Holz, Bielsky, & Schneider, 2014; World Health Organization, 2009). The extent of extrapolation that is permitted varies among regulatory agencies and is assessed on a case-by-case basis (Daller, 2016; Socinski et al., 2015). The purpose is to reduce or eliminate the need for unnecessary clinical studies of the biosimilar in multiple indications that are already approved for the originator. The EMA, FDA, and WHO regulatory guidelines permit extrapolation provided that there is appropriate scientific justification and the totality of evidence demonstrates biosimilarity (European Medicines Agency, 2014; US Food and Drug Administration, 2015b; World Health Organization, 2009). The mechanism of action of the biologic across the different indications concerned is a key consideration.

Several biosimilars approved in Europe, such as those for filgrastim, epoetin, bevacizumab, trastuzumab, and infliximab, have been successfully approved in multiple indications on the basis of extrapolation (European Medicines Agency, 2018b; Weise et al., 2014). Similarly, in the United States, extrapolation has allowed biosimilars for adalimumab, etanercept, filgrastim, bevacizumab, trastuzumab, epoetin, and infliximab to be licensed for use in multiple indications (US Food and Drug Administration, 2015a, 2016b, 2016c, 2016d, 2018).

Interchangeability

Interchangeability is the concept that two products can be exchanged one for another without a significant risk of harm to the patient (Daller, 2016; Renwick, Smolina, Gladstone, Weymann, & Morgan, 2016; Rugo et al., 2016; Socinski et al., 2015; Weise et al., 2012). Automatic substitution is the practice by which a product other than the one prescribed is dispensed at the pharmacy lev-

el without the consent of the prescriber (Daller, 2016; Renwick et al., 2016; Rugo et al., 2016; Socinski et al., 2015; Weise et al., 2012).

There are no recommendations from the EMA regarding interchangeability, and it is instead the responsibility of individual member states (Rugo et al., 2016). Many of these countries have prohibited automatic substitution (Renwick et al., 2016). In the United States, individual state laws will apply to interchangeability and automatic substitution (Renwick et al., 2016). However, recent FDA draft guidance has stated that a biologic product may be considered interchangeable if the product "can be expected to produce the same clinical result as the reference product in any given patient" and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" (US Food and Drug Administration, 2017a). The data required to support these criteria can vary based on a number of factors, including product complexity, product-specific immunogenicity, and available postmarketing data. The FDA recommends that developers of an interchangeable medicine work with the FDA to determine a suitable product development plan needed to support demonstration of interchangeability (US Food and Drug Administration, 2017a). Consequently, interchangeability is approved on a case-by-case basis.

Interchangeability determinations may have implications for patients, clinicians, and health-care systems. Therefore, one suggestion is that health-care system frameworks include operational and educational guidance on biosimilars, including guidance on alternating or switching between products (e.g., for oncology drugs, the acute dosing schedule may mean that initiating treatment with a biosimilar may be more acceptable than switching therapies mid-course), communicating product changes to other health-care providers and patients, strategies to distinguish between biosimilars and originator products, and opt-out provisions (Dombrowski, 2013; Lucio, Stevenson, & Hoffman, 2013).

Pharmacovigilance

Pharmacovigilance refers to the detection, assessment, and prevention of adverse effects after a product is launched onto the market (Daller, 2016; Dombrowski, 2013; Rugo et al., 2016; Socinski et al., 2015). As with all biologics, postmarketing pharmacovigilance is critical to monitor the safety of biosimilars, particularly due to their complexity and unique manufacturing and development processes, and will take the form of risk management plans and other pharmacovigilance protocols (Daller, 2016; Dombrowski, 2013; Rugo et al., 2016; Socinski et al., 2015). Advanced practice providers play an important role in the long-term monitoring and assessment of medicinal products within the clinic; thus, distinct and unique names for biosimilars will help support pharmacovigilance efforts. Furthermore, pharmacovigilance is necessary to monitor and assess rare adverse events or immunogenicity that may not be detected during the clinical trial stages (Daller, 2016; Dombrowski, 2013; Rugo et al., 2016; Socinski et al., 2015). Therefore, advanced practice providers are critical to ensuring long-term patient safety in clinical practice and should report any suspected adverse events or drug reactions, as well as identify the specific product that is causing the event/reaction, whether it is the biosimilar or the originator product.

Other Practical Considerations

Due to the sensitivity and complexity of the biosimilar manufacturing process, awareness of a manufacturer's handling practices and history of recalls associated with product quality is essential to ensure drug efficacy and patient safety (Crommelin et al., 2005; Daller, 2016; Dombrowski, 2013; Griffith, McBride, Stevenson, & Green, 2014; Kuhlmann & Covic, 2006; Schellekens, 2009). Furthermore, biologics are often administered to patients in local hospitals or physician offices; therefore, it is important to consider the logistics for products in these settings (Griffith et al., 2014). For example, proper drug storage and handling/administration, product availability, supply chain security, and the ability to discriminate between products are critical to ensure patient care, product integrity, and effective long-term safety monitoring in the clinical practice setting (Griffith et al., 2014).

Manufacturer-provided support services represent another potential area of differentiation between biosimilars and originator products, or indeed between various biosimilars, including

tools for reducing administrative burden, patient education offerings, and prefilled syringes to improve patient efficiencies. Therefore, in order to remain informed and provide the best possible care and treatment options to their patients, it is vital that advanced practice providers participate in pharmacy and therapeutics committees and continue to play an active role in the assessment and inclusion of biosimilar products within their local formulary. Additionally, it is important that advanced practice providers assist with ensuring that both patients and other health-care providers are made aware of any changes in treatment plans, i.e., switching from an originator product to a biosimilar, or switching between biosimilars. Furthermore, advanced practice providers should be vigilant when both biosimilars and originator products are available within their clinic to ensure appropriate safety monitoring and tracking of any potential adverse events and drug reactions, as well as to be aware of any differences in the storage or availability of these products, in order to mitigate potential issues with product quality or supply.

Pricing

Although biosimilars are less costly than the corresponding originator products, the discounts (reported to be approximately 30% in Europe; Blackstone and Joseph, 2013) are typically not as marked down as those observed with small-molecule generic drugs. This is predominantly due to the overall cost of biosimilar development (Bennett et al., 2014; Danzon, 2014; Dombrowski, 2013; Renwick et al., 2016). Price regulation and reimbursement concerning biosimilars can vary between countries and, within the United States, these will vary based on the setting of administration, prescription drug coverage, and local policies (Bennett et al., 2014; Danzon, 2014; Dombrowski, 2013; Renwick et al., 2016). In the community setting, medication decisions are often based on cost, patient reimbursement policies, and individual insurance plans. Therefore, it is important that advanced practice providers be involved in the treatment decision-making process, are aware of when patients are on biosimilars or originator products in order to monitor for any differences in clinical responses or toxicities, and remain informed regarding the treatment choices available to their patients.

SUMMARY

Biosimilars have the potential to substantially impact patient care by reducing costs and expanding access to biologic therapies. As more biosimilars are approved and become available, advanced practice providers will be at the forefront of treatment decisions involving biosimilars, addressing queries from patients and other health-care providers regarding biosimilars, and managing the successful integration of biosimilars into clinical practice. Therefore, it is important that advanced practice providers understand the developmental and regulatory process concerning biosimilars, the key practical considerations for biosimilars, and the importance of biosimilars in improving access to biologic therapies in clinical practice.

Acknowledgment

Medical writing support was provided by Anne Marie Reid, PhD, of Engage Scientific Solutions and was funded by Pfizer Inc.

Disclosure

Dr. Tinsley has served on speakers bureaus for Incyte and Novartis, has served on the speakers bureau and acted as a consultant for Celgene, and has participated in nurse advisory boards for Amgen and Genentech. Ms. Grande, Ms. Olson, and Ms. Plato have participated in advisory boards for Pfizer Inc. Mr. Jacobs is an employee of Pfizer Inc.

References

Baer, W. H., II., Maini, A., & Jacobs I. (2014). Barriers to the access and use of rituximab in patients with non-hodgkin's lymphoma and chronic lymphocytic leukemia: A physician survey. *Pharmaceuticals, 7*(5), 530–544. https://doi.org/10.3390/ph7050530

Bennett, C. L., Chen, B., Hermanson, T., Wyatt, M. D., Schulz, R. M., Georgantopoulos, P.,...Armitage, J. O. (2014). Regulatory and clinical considerations for biosimilar oncology drugs. *Lancet Oncology, 15*(13), e594–e605. https://doi.org/10.1016/S1470-2045(14)70365-1

Berkowitz, S. A., Engen, J. R., Mazzeo, J. R., & Jones, G. B. (2012). Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. *Nature Reviews Drug Discovery, 11*(7), 527–540. https://doi.org/10.1038/nrd3746

Biogen. (2016). Flixabi®, Biogen's infliximab biosimilar referencing Remicade®, approved in the European Union. Retrieved from http://investors.biogen.com/news-releases/news-release-details/flixabir-biogens-infliximab-biosimilar-referencing-remicader

Blackstone, E. A., & Joseph, P. F. (2013). The economics of biosimilars. *American Health and Drug Benefits, 6*(8), 469–478.

Camacho, L. H., Frost, C. P., Abella, E., Morrow, P. K., & Whittak-

er, S. (2014). Biosimilars 101: Considerations for U.S. oncologists in clinical practice. *Cancer Medicine, 3*(4), 889–899. https://doi.org/10.1002/cam4.258

Cohen, H., Beydoun, D., Chien, D., Lessor, T., McCabe, D., Muenzberg, M.,...Uy, J. (2017) Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Advances in Therapy, 33*(12), 2160–2172. https://doi.org/10.1007/s12325-016-0431-5

Crommelin, D., Bermejo, T., Bissig, M., Damiaans, J., Krämer, I., Rambourg, P.,...Tredree R. (2005). Pharmaceutical evaluation of biosimilars: Important differences from generic low-molecular-weight pharmaceuticals. *European Journal of Hospital Pharmacy Science and Practice, 11*(1), 11–17.

Daller, J. (2016). Biosimilars: A consideration of the regulations in the United States and European Union. *Regulatory Toxicology and Pharmacology,* 76, 199–208. https://doi.org/10.1016/j.yrtph.2015.12.013

Danzon, P. M. (2014). Pricing and reimbursement of biopharmaceuticals and medical devices in the USA. In A. J. Culyer (Ed.), *Encyclopedia of Health Economics* (pp 127–135). York, UK: Elsevier Inc.

Declerck, P., Danesi, R., Petersel, D., & Jacobs, I. (2017). The language of biosimilars: Clarification, definitions, and regulatory aspects. *Drugs, 77*(6), 671–677. https://doi.org/10.1007/s40265-017-0717-1

Dolinar, R. O., & Reilly, M. S. (2014). Biosimilars naming, label transparency and authority of choice – survey findings among European physicians. *Generics and Biosimilars Initiative Journal, 3*(2), 58–62. https://doi.org/10.5639/gabij.2014.0302.018

Dombrowski, S. R. (2013). A health-system pharmacist's guide to biosimilars: Regulatory, scientific, and practical considerations. Retrieved from http://ashpadvantagemedia.com/downloads/biosimcentral_guidelines.pdf

European Medicines Agency. (2012). QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127589.pdf

European Medicines Agency. (2013). European Medicines Agency recommends approval of first two monoclonal-antibody biosimilars. Retrieved from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001837.jsp&mid=WC0b01ac058004d5c1

European Medicines Agency. (2014). Guideline on similar biological medicinal products. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

European Medicines Agency. (2017a). Biosimilars in the EU: Information guide for healthcare professionals. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

European Medicines Agency. (2017b). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 23-26 January 2017. Retrieved from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/01/news_detail_002682.jsp&mid=WC0b01ac058004d5c1

European Medicines Agency. (2018a). EU Clinical Trials Register. Retrieved from https://www.clinicaltrialsregister.eu/

European Medicines Agency. (2018b). European public assessment reports by type (biosimilars). Retrieved from https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised-36/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar

Generics and Biosimilars Initiative (GaBI) Online. (2012). Biosimilar monoclonal antibody approved in Korea. Retrieved from http://www.gabionline.net/Biosimilars/News/Biosimilar-monoclonal-antibody-approved-in-Korea

Generics and Biosimilars Initiative (GaBI) Online. (2014). Biosimilar infliximab launched in Japan. Retrieved from http://www.gabionline.net/Biosimilars/News/Biosimilar-infliximab-launched-in-Japan

Global Market Insights. (2016). Cancer biological therapy market size worth USD 100 billion by 2023: Global Market Insights Inc. Retrieved from http://www.prnewswire.com/news-releases/cancer-biological-therapy-market-size-worth-usd-100-billion-by-2023-global-market-insights-inc-589056961.html

Griffith, N., McBride, A., Stevenson, J. G., & Green, L. (2014). Formulary selection criteria for biosimilars: Considerations for US health-system pharmacists. *Hospital Pharmacy, 49*(9), 813–825. https://doi.org/10.1310/hpj4909-813

Hallersten, A., Fürst, W., & Mezzasalma, R. (2016). Physicians prefer greater detail in the biosimilar label (SmPC) - Results of a survey across seven European countries. *Regulatory Toxicology and Pharmacology, 77*, 275–281. https://doi.org/10.1016/j.yrtph.2016.03.021

Health Canada. (2016). Guidance for sponsors: Information and submission requirements for biosimilar biologic drugs. Retrieved from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf

Hemmington, A., Dalbeth, N., Jarrett, P., Fraser, A. G., Broom, R., Browett, P., & Petrie, K. J. (2017). Medical specialists' attitudes to prescribing biosimilars. *Pharmacoepidemiology and Drug Safety, 26*(5), 570–577. https://doi.org/10.1002/pds.4186

IMS Institute for Healthcare Informatics. (2016a). Delivering on the potential of biosimilar medicines: The role of functioning competitive markets. Retrieved from http://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf

IMS Institute for Healthcare Informatics. (2016b). Medicines use and spending in the US: A review of 2015 and outlook to 2020. Retrieved from https://morningconsult.com/wp-content/uploads/2016/04/IMS-Institute-US-Drug-Spending-2015.pdf

Kuhlmann, M., & Covic A. (2006). The protein science of biosimilars. *Nephrology, Dialysis, Transplantation*, 21(suppl 5), v4–v8. https://doi.org/10.1093/ndt/gfl474

Lammers, P., Criscitiello, C., Curigliano, G., & Jacobs, I. (2014). Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the United States and emerging markets. *Pharmaceuticals (Basel), 7*(9), 943–953. https://doi.org/10.3390/ph7090943

Lucio, S. D., Stevenson, J. G., & Hoffman, J. M. (2013). Biosimilars: Implications for health-system pharmacists. *American Journal of Health-System Pharmacy, 70*(22), 2004–2017. https://doi.org/10.2146/ajhp130119

Mayden, K. D., Larson, P., Geiger, D., & Watson, H. (2015). Biosimilars in the United States: Considerations for oncology

advanced practitioners. *Journal of the Advanced Practitioner in Oncology, 6*(2), 108–116. https://doi.org/10.6004/jadpro.2015.6.2.3

McCamish, M., & Woollett, G. (2012). The state of the art in the development of biosimilars. *Clinical Pharmacology and Therapeutics, 91*(3), 405–417. https://doi.org/10.1038/clpt.2011.343

Ministry of Health Labour and Welfare. (2013). Guideline for the quality, safety, and efficacy assurance of follow-on biologics. Retrieved from http://www.pmda.go.jp/files/000153851.pdf

Molinari, A. L., Gewanter, H. L., Loaiza-Bonilla, A., Reilly, M., Kennedy, B., & Charles D. (2016). Global survey of physicians' attitudes toward biologic and biosimilar therapies. *Journal of Clinical Oncology*, 34(15 suppl), e18025–e18025. https://doi.org/10.1200/JCO.2016.34.15_suppl.e18025

Monk, B. J., Lammers, P. E., Cartwright, T., & Jacobs I. (2017). Barriers to the access of bevacizumab in patients with solid tumors and the potential impact of biosimilars: A physician survey. *Pharmaceuticals (Basel), 10*(1), 19. https://doi.org/10.3390/ph10010019

National Cancer Institute. (2016). Biological therapies for cancer. Retrieved from https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet

Pasina, L., Casadei, G., & Nobili, A. (2016). A survey among hospital specialists and pharmacists about biosimilars. *European Journal of Internal Medicine, 35*, e31–e33. https://doi.org/10.1016/j.ejim.2016.07.010

Philippidis, A. (2014). Biosimilars: 11 drugs to watch. Retrieved from http://www.genengnews.com/insight-and-intelligence/biosimilars-11-drugs-to-watch/77900135

Rak Tkaczuk, K. H., & Jacobs, I. A. (2014). Biosimilars in oncology: From development to clinical practice. *Seminars in Oncology*, 41(suppl 3), S3–S12. https://doi.org/10.1053/j.seminoncol.2014.03.008

Renwick, M. J., Smolina, K., Gladstone, E. J., Weymann, D., & Morgan, S. G. (2016). Postmarket policy considerations for biosimilar oncology drugs. *Lancet Oncology, 17*(1), e31–e38. https://doi.org/10.1016/S1470-2045(15)00381-2

Rugo, H. S., Linton, K. M., Cervi, P., Rosenberg, J. A., & Jacobs, I. (2016). A clinician's guide to biosimilars in oncology. *Cancer Treatment Reviews, 46*, 73–79. https://doi.org/10.1016/j.ctrv.2016.04.003

Schellekens, H. (2009). Biosimilar therapeutics—what do we need to consider? *NDT Plus, 2*(suppl 1), i27–i36. https://doi.org/10.1093/ndtplus/sfn177

Singh, S. K. (2011). Impact of product-related factors on immunogenicity of biotherapeutics. *Journal of Pharmaceutical Sciences, 100*(2), 354–387. https://doi.org/10.1002/jps.22276

Socinski, M. A., Curigliano, G., Jacobs, I., Gumbiner, B., MacDonald, J., & Thomas, D. (2015). Clinical considerations for the development of biosimilars in oncology. *mAbs, 7*(2), 286–293. https://doi.org/10.1080/19420862.2015.1008346

US Food and Drug Administration. (2015a). FDA approves first biosimilar product Zarxio. Retrieved from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm

US Food and Drug Administration. (2015b). Scientific considerations in demonstrating biosimilarity to a reference product: Guidance for industry [Report]. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

US Food and Drug Administration. (2016a). Abbreviated New Drug Application (ANDA): Generics. Retrieved from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/

US Food and Drug Administration. (2016b). FDA approves Amjevita, a biosimilar to Humira. Retrieved from http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm522243.htm

US Food and Drug Administration. (2016c). FDA approves Erelzi, a biosimilar to Enbrel. Retrieved from http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518639.htm

US Food and Drug Administration. (2016d). FDA approves Inflectra, a biosimilar to Remicade. Retrieved from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm

US Food and Drug Administration. (2016e). Labeling for biosimilar products. Guidance for industry. Retrieved from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf

US Food and Drug Administration. (2017a). Considerations in demonstrating interchangeability with a reference product: Guidance for industry. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf

US Food and Drug Administration. (2017b). FDA approves first biosimilar for the treatment of cancer. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576112.htm

US Food and Drug Administration. (2017c). Nonproprietary naming of biological products: Guidance for industry. Retrieved from http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf

US Food and Drug Administration. (2018). Center for Drug Evaluation and Research: List of licensed biological products with (1) reference product exclusivity and (2) biosimilarity or interchangeability evaluations to date. Retrieved from https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf

US National Library of Medicine. (2018). ClinicalTrials.gov. Retrieved from https://clinicaltrials.gov/

Weise, M., Bielsky, M. C., De Smet, K., Ehmann, F., Ekman, N., Giezen, T. J.,...Schneider C. K. (2012). Biosimilars: What clinicians should know. *Blood, 120*(26), 5111–5117. https://doi.org/10.1182/blood-2012-04-425744

Weise, M., Bielsky, M. C., De Smet, K., Ehmann, F., Ekman, N., Narayanan, G.,...Schneider C. K. (2011). Biosimilars—why terminology matters. *Nature Biotechnology, 29*(8), 690–693. https://doi.org/10.1038/nbt.1936

Weise, M., Kurki, P., Wolff-Holz, E., Bielsky, M. C., & Schneider, C. K. (2014). Biosimilars: The science of extrapolation. *Blood, 124*(22), 3191–3196. https://doi.org/10.1182/blood-2014-06-583617

World Health Organization. (2009). Guidelines on evaluation of similar biotherapeutic products (SBPs) [Report]. Retrieved from http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

World Health Organization. (2018). International Clinical Trials Registry Platform (ICTRP). Retrieved from http://www.who.int/ictrp/en/