review article

Improving Access to Cancer Treatments: The Role of Biosimilars

abstract

Biologics play a key role in cancer treatment and are principal components of many therapeutic regimens. However, they require complex manufacturing processes, resulting in high cost and occasional shortages in supply. The cost of biologics limits accessibility of cancer treatment for many patients. Effective and affordable cancer therapies are needed globally, more so in developing countries, where health care resources can be limited. Biosimilars, which have biologic activity comparable to their corresponding reference drugs and are often more cost effective, have the potential to enhance treatment accessibility for patients and provide alternatives for decision makers (ie, prescribers, regulators, payers, policymakers, and drug developers). Impending patent expirations of several oncology biologics have opened up a vista for the development of corresponding biosimilars. Several countries have implemented abbreviated pathways for approval of biosimilars; however, challenges to their effective use persist. Some of these include designing appropriate clinical trials for assessing biosimilarity, extrapolation of indications, immunogenicity, interchangeability with the reference drug, lack of awareness and possibly acceptance among health care providers, and potential political barriers. In this review, we discuss the potential role and impact of biosimilars in oncology and the challenges related to their adoption and use. We also review the safety and efficacy of some of the widely used biosimilars in oncology and other therapeutic areas (eg, bevacizumab, darbepoetin, filgrastim, rituximab, and trastuzumab).

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INTRODUCTION

Biologics are important components of the modern cancer treatment armamentarium[1] and are recommended for the treatment of various types of cancers by National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) guidelines because they improve clinical outcomes, including overall survival (OS).[2,3] Although only 15% of the agents listed in the NCCN Drugs and Biologics Compendium are biologics, they account for the majority of drug-related expenditures in outpatient and hospital settings in the United States.[2] According to a 2011 drug expenditure analysis, biologics accounted for approximately 55% of the total expenditure on antineoplastic drugs in the US health care system; among the biologics, bevacizumab (Avastin; Roche, Basel, Switzerland), rituximab (Rituxan/MabThera; Roche), and trastuzumab (Herceptin; Roche) accounted for more than half of the top 20 antineoplastic expenditures in outpatient clinics.[1,2,4,5] Bevacizumab is approved for the treatment of colorectal, brain, lung, fallopian tube, renal, and other cancers[6]; rituximab is approved for the treatment of CD20-positive non-Hodgkin lymphoma and leukemia[7]; and trastuzumab is approved for the treatment of human epidermal growth factor receptor 2 (HER2) –positive breast cancer and metastatic gastric and gastroesophageal junction adenocarcinomas.[8] Although effective, biologics are expensive because of the complex manufacturing and development processes, adding to the already high cost associated with cancer treatment.

Over the last few years, biosimilars have generated great interest worldwide as effective alternatives to biologics. The US Public Health Service Act [Section 351(i)] defines a biosimilar as a "biologic product that is highly similar to the reference biologic, notwithstanding minor differences in clinically inactive components."[9(p282)] Similarly, the European Union defines a biosimilar medicine as a medicinal product, which is a copy of a biologic product (the reference product) that has already received authorization.[10] Biosimilars are also referred to as follow-on biologicals, similar biotherapeutic products, or subsequent-entry biologics.[11] The term biogenerics is also used occasionally but should be avoided because it may imply that biosimilars are identical to the original compounds, as in the case of generic versions of small-molecule drugs.[10]

Biosimilars have been integral to clinical practice in the European Union for almost a decade. In 2006, somatropin (ribosomal DNA origin) for injection (Omnitrope; Sandoz, Basel, Switzerland; reference drug, Genotropin; Pfizer, New York, NY) became the first biosimilar to be approved by the European Medicines Agency (EMA),[12] followed by biosimilars for epoetin alfa (Epoetin Alfa Hexal; Hexal, Holzkirchen, Germany; reference drug, Eprex/Erypo; Janssen Pharmaceuticals, Raritan, NJ)[13] in 2007 and filgrastim (Zarxio; Sandoz; reference drug, Neupogen; Amgen, Thousand Oaks, CA) in 2009.[1,14] In 2015, Zarxio became the first biosimilar to be approved by the US Food and Drug Administration (FDA).[15] Several key oncology biologics have already lost or will soon lose market exclusivity (Table 1),[16,17] and corresponding biosimilars are currently in various stages of development (Table 2).[16]

Expanding patient access to effective therapeutic agents and reducing health care costs continue to be the two main driving factors behind the rapid development of biosimilars. As we discuss in detail in this review, many oncology biosimilars have demonstrated similar clinical efficacy to their reference drugs.[18-21] Common examples include biosimilars for filgrastim, pegfilgrastim,[19,20,22] rituximab, and trastuzumab.[21] Efficacy and safety of some biosimilars have also been tested in real-world settings with encouraging results.[23] Such studies have prompted regulatory bodies to adopt a more positive opinion of biosimilars, even in highly regulated markets, paving the way for future inclusion of biosimilars in oncology therapy.[24] As a result, global biosimilar sales are expected to rise from US$2.29 billion in 2015 to US$6.22 billion by 2020.[25]

GUIDANCE ON BIOSIMILAR DEVELOPMENT

To demonstrate biosimilarity, the WHO recommends conducting characterization and comparability studies on physicochemical properties, biologic activity, process- or product-related impurities, and product stability, in addition to nonclinical studies on in vitro and in vivo bioactivity, and clinical studies on pharmacokinetics (PKs) and pharmacodynamics (PDs), efficacy, and safety (Fig 1).[26-28] According to a recent analysis, the leading biosimilar specialists in the world are located in the United States, Europe, and Israel, with other important players being India, China, and Brazil.[29,30] Regulatory guidance for biosimilar development in these nations broadly follows similar principles, with a few minor differences; these guidelines have been summarized in Table 3. Approval of biosimilars by the FDA, Health Canada, and the EMA requires in vitro studies demonstrating similarity to a reference biologic in terms of quality and nonclinical and clinical studies demonstrating comparable PKs, efficacy, safety, and immunogenicity.[31,36,37] The Biologics Price Competition and Innovation (BPCI) Act of 2009[38] authorizes the FDA to allow an abbreviated pathway for approval of biosimilars, which eliminates unnecessary testing of biosimilars in animals and humans, thus saving time, money, and manpower. The US Patient Protection and Affordable Care Act of 2010 also supports the abbreviated pathway.[39]

In developing countries such as India, efforts are focused on developing biosimilars involving low development costs and risks. Consequently, comprehensive regulatory guidelines are in place to monitor the development and approval of biosimilar products in India.[34] Currently, India is the world's second-largest supplier of vaccines and fourth-largest supplier of pharmaceuticals[27] and is emerging as a global leader in manufacturing and use of biosimilars. Many biosimilars have already been approved and marketed in India for various types of cancer (Table 4).[39,40] Indian regulatory authorities have recently proposed revised guidelines for the development of biosimilars in India,[41] requiring specific postmarketing single-arm safety studies to be conducted among at least 200 evaluable patients, followed by comparison of results with historical data on the reference drug. These phase IV studies should be completed within 2 years of marketing approval and should have safety as their primary end point, with efficacy and immunogenicity as secondary end points.[42]

PHARMACOECONOMIC IMPACT OF BIOSIMILARS IN ONCOLOGY

The global annual economic burden of cancer, including costs associated with prevention, treatment, and disability-adjusted life-years lost

Table 1. Approval and Patent Expiration Dates for Important Oncology Biologics

	United States		European Union	
Drug	**Approval**	**Patent Expiration**	**Approval**	**Patent Expiration**
Bevacizumab	2004	2019	2005	2022
Cetuximab	2004	2018	2004	2014
Darbepoetin alfa	2001	2024	2001	2016
Epoetin alfa	1998	2013	—	—
Filgrastim	1991	2013	—	—
Pegfilgrastim	2002	2015	2002	2017
Rituximab	1997	2016	1998	2013
Trastuzumab	1998	2019	2000	2014

Table 2. Examples of Most Widely Used Biosimilars in Various Stages of Development Globally

Original Drug	Biosimilar	Manufacturer
Bevacizumab	ABP 215	Amgen, Thousand Oaks, CA
	BCD-021	BIOCAD, Moscow, Russia
	Bevacirel	Reliance Life Sciences, Mumbai, India
	BI 695502	Boehringer Ingelheim, Ingelheim am Rhein, Germany
	Cizumab	Hetero Drugs, Hyderabad, India
	DRL_BZ	Dr Reddy's Laboratories, Hyderabad, India
	PF-06439535	Pfizer, New York, NY
	SB8	Samsung Bioepis, Incheon, Republic of Korea
Rituximab	ABP 798	Amgen
	BCD-020	BIOCAD
	GP2013	Novartis, Basel, Switzerland
	MabionCD20	Mabion, Konstantynów Łódzki, Poland
	MK-8808	Merck, Kenilworth, NJ
	PF-05280586	Pfizer
	RTXM83	mAbxience, Lugano, Switzerland
Trastuzumab	ABP 980	Amgen
	BCD-022	BIOCAD
	CT-P6	Celltrion, Incheon, Republic of Korea
	DRL_TZ	Dr Reddy's Laboratories
	MYL-1401O	Mylan, Amsterdam, the Netherlands
	PF-05280014	Pfizer
	SB3	Samsung Bioepis

to cancer, was estimated at US$1.16 trillion in 2010.[43,44] When longer-term costs to patients and their families were taken into account, this estimate increased to US$2.5 trillion.[44] In developing countries such as India, where nearly 70% of the population pays for their own health care,[45] patients are less likely to have access to expensive oncology treatments.[46] Most often, the cost of cancer treatments exceeds the average per capita income by many multiples. For example, the cost of a typical trastuzumab course, prescribed during the treatment of metastatic breast cancer, is approximately 15 times the per capita monthly income of an average Indian.[45] Similarly, trastuzumab treatment in Peru costs more than three times the gross domestic product per capita per disability-adjusted life-year and cannot be considered cost effective.[47]

Until a few years ago, pharmaceutical and economic market analysts often expected that biosimilars would cost up to 30% less than their reference drugs.[10,48] For example, in the United States, the cost of filgrastim-sndz is 15% less than Neupogen, and this price difference is expected to increase further.[49] Similarly, biosimilar recombinant human erythropoietin costs 25% to 30% less than its reference drug in the European Union.[1] In recent years, however, cost savings as high as 70% have been observed with the use of biosimilars. For example, in Norway, an infliximab biosimilar was initially offered at a 39% discount over the originator drug, but it failed to gain a significant proportion of the market; subsequently, it was discounted by nearly 70% and now represents more than 50% of drug sales.[50,51] Recently, a similar 70% discount was offered for the same biosimilar in Denmark.[52] In India and Peru, a rituximab biosimilar (Reditux; Dr Reddy's Laboratories, Hyderabad, India) was introduced for the same indications as the originator drug at a 50% lower price.[53] These trends illustrate the potentially massive impact of biosimilars on oncology care at the levels of the patient and the industry as a whole.

The cost-saving potential of biosimilars will also vary according to the pricing of the original biologic, its sales, the degree of competition, and

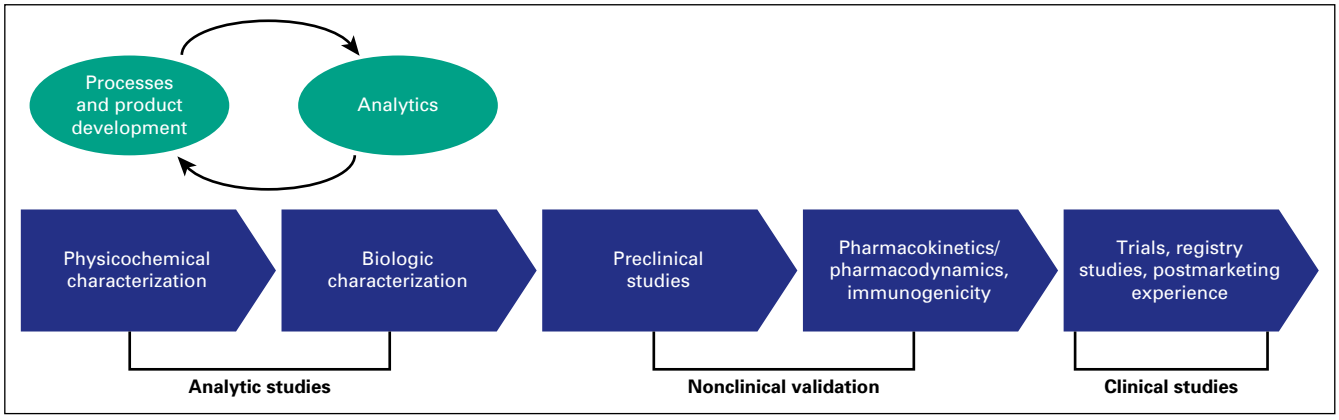

Fig 1. Approval process for biosimilars. Data adapted.[26]

Table 3. Key Points of Various Regulatory Guidelines on Biosimilar Development

Parameter	FDA[1,31]	EMA[28,32]	Israel[33]	India[34,35]	China[35]	Brazil[35]
Data requirements	Uses a risk-based, totality-of-evidence approach when evaluating biosimilarity; stepwise approach, including detailed structural and functional characterizations of the biosimilar and reference biologic, is recommended	Guiding principle is to establish similarity to ensure previously proven safety and efficacy of the reference biologic apply to the biosimilar; stepwise approach, including detailed structural and functional characterizations of the biosimilar and reference biologic, is recommended	Registrations of the biosimilar with FDA, EMA, Canada, Australia, New Zealand, Japan, or Swiss Agency for Therapeutic Products (Swissmedic) may constitute a basis for registration in Israel	Conduct of analytic and quality characterization studies, nonclinical studies (PDs, cell proliferation, immunogenicity, and ⩾ one repeat dose toxicity), and clinical studies (PKs/PDs, comparative, immunogenicity) is required; for clinical studies, equivalence study design is preferred over noninferiority	Conduct of analytic and quality characterization studies, nonclinical studies (PKs/PDs, immunogenicity), and clinical studies (PKs/PDs, immunogenicity) is required	Conduct of analytic and quality characterization studies, nonclinical studies (PDs, cumulative toxicity), and clinical studies (PKs/PDs, comparative, immunogenicity) is required
Extrapolations	Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same; any differences do not necessarily preclude extrapolation and are considered in context of totality of evidence	Extrapolation is permitted based only on comparability data; if pivotal evidence for comparability is based on PDs and different mechanisms of action are relevant for the claimed indications (or uncertainty exists), then additional relevant data will need to be provided	Extrapolation to indications for which the biosimilar was not clinically tested is permitted provided the reference drug is registered for such indications on the basis of the totality of available information, including quality, safety, and efficacy data, with emphasis on mechanism of action	Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same	Extrapolations are considered on a case-by-case basis	Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same and safety and immunogenicity have been sufficiently characterized
Reference drug	Reference drug should be licensed by FDA	Reference drug should be registered in a country where approval for the biosimilar is sought; reference product registered in a different country may be used with some additional studies	Registration of the biosimilar will not be permitted if the reference drug is not registered in Israel	Reference drug should be licensed in India and be an innovator drug; if reference biologic is not marketed in India, then it should be licensed for 4 years postapproval in innovator jurisdiction in a country with well-established regulatory framework	Reference drug should be approved by Chinese regulatory agencies; another biosimilar (even if approved) cannot be considered as a reference drug	Reference drug should be registered in Brazil or another country with regulatory requirements similar to those of Brazil
Interchangeability	More-specific guidelines for demonstration of interchangeability are available	No provision for interchangeability in most EU geographies	Physician, upon consultation with the medical institution, is permitted to substitute a reference drug with its biosimilar for the same indications	Recommendations on interchangeability are not available	Recommendations on interchangeability are not available	Recommendations on interchangeability are not available
Other points	Full clinical program can be skipped if extensive structural and functional similarities are demonstrated; comparative clinical studies must demonstrate purity, potency, immunogenicity, and safety in a condition for which the reference biologic is approved	Standalone development of the product should be considered if significant differences between the biosimilar and reference biologic become apparent	Risk management plan or risk evaluation and mitigation strategies need to be submitted as part of the application for registration of a biosimilar		Amino acid sequence of the biosimilar and its reference must be same	

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic.

Table 4. Biosimilars Approved and Marketed in India

Product Name	Therapeutic Area	Approval or Launch Date in India	Manufacturer
Darbepoetin alfa			
Actorise	Anemia, cancer, chronic kidney failure	2014	Cipla/Hetero Drugs
Cresp	Anemia, cancer, chronic kidney failure	2010	Dr Reddy's Laboratories
Darbatitor	Anemia, cancer, chronic kidney failure	2014	Torrent Pharmaceuticals
Epoetin alfa			
Ceriton	Anemia, cancer, chronic kidney failure	NA	Ranbaxy
Epofer	Anemia, cancer, chronic kidney failure	NA	Emcure
Epofit/Erykine	Anemia, cancer, chronic kidney failure	2005	Intas Pharmaceuticals
Epotin	Anemia, cancer, chronic kidney failure	NA	Claris Lifesciences
Erypro	Anemia, cancer, chronic kidney failure	NA	Biocon
Relipoietin	Anemia, autologous blood transfusion, chronic kidney failure, HIV	2008	Reliance Life Sciences
Wepox	Anemia, cancer, chronic kidney failure	2001	Wockhardt
Filgrastim			
Colstim	Neutropenia	2013	Cadila Pharmaceutical
Emgrast	Cancer, neutropenia	2010	Gennova Biopharmaceuticals (Emcure)
Fegrast	Cancer, hematopoietic stem-cell transplantation, neutropenia	NA	Claris Lifesciences
Filgrastim	Neutropenia	2013	USV
Grafeel	Neutropenia, hematopoietic stem-cell transplantation, cancer	2001	Dr Reddy's Laboratories
Lupifil	Neutropenia	2013	Lupin
Neukine	Neutropenia, hematopoietic stem-cell transplantation, cancer	2004	Intas Pharmaceuticals
Nufil	Cancer, neutropenia	NA	Biocon
Religrast	Neutropenia	2008	Reliance Life Sciences
Peg-filgrastim			
Lupifil-P	Cancer, neutropenia	2013	Lupin
Neupeg	Cancer, neutropenia	2007	Intas Pharmaceuticals
Pegex	Cancer, neutropenia	2010	Gennova Biopharmaceuticals (Emcure)
Peg-Grafeel	Chemotherapy-induced febrile neutropenia	2011	Dr Reddy's Laboratories
Rituximab			
Maball	Lymphoma, NHL	2015	Hetero Drugs
MABTAS	Lymphoma, NHL	2013	Intas Pharmaceuticals
Reditux	Leukemia, lymphoma, rheumatoid arthritis	2007	Dr Reddy's Laboratories
Rituximab	NHL	2013	Zenotech Laboratories
RituxiRel	NHL, rheumatoid arthritis	2015	Reliance Life Sciences
Trastuzumab			
CanMab	Breast cancer	2013	Biocon

Abbreviations: NA, not available; NHL, non-Hodgkin lymphoma.

so on.[54] A recent cost-benefit analysis of various biosimilars was performed assuming a year-on-year originator growth of 10%, an increase in the share of originator sales exposed to biosimilar competition from 10% in year 1 to 20% in year 10, biosimilar market penetration of 60%, and a biosimilar price discount of 35% resulting from competition. Results indicated that potential direct cost savings of US$44.2 billion were expected over a 10-year period from 2014 to 2024 (Table 5). The highest

Table 5. Potential Cost Savings Likely to Be Offered by Various Biosimilars by 2024[54]

Drug Class	Potential Cost Savings (%)
Anti-TNF products	21
Long-acting insulins	15
Monoclonal antibody antineoplastics	13
Fast-acting insulins	11
Colony-stimulating factors	6
Interferons	6
Erythropoietin products	6
Immunostimulants (excluding interferons)	5

Abbreviation: TNF, tumor necrosis factor.

cost savings are expected from anti–tumor necrosis factor products. However, more systematic strategies need to be used to estimate the magnitude of clinical benefit of biosimilars across geographies and economies; these could include the use of tools such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale.[55] This scale is a validated and reproducible scale designed to assess the magnitude of clinical benefit for cancer medicines. This scale uses a rational, structured, and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anticancer treatment. Use of such approaches can provide a more accurate estimate of the cost benefit of biosimilars.

CHALLENGES IN THE ADOPTION AND USE OF BIOSIMILARS

Although biosimilars hold the promise of being effective and safe alternatives to biologics, several challenges impede their adoption and use. For example, designing appropriate clinical trials with relevant end points for testing comparability can be difficult. Likewise, generating clinician and patient interest in enrolling for such trials is a challenge in itself, because novel drugs offer the possibility of increased disease control and therefore tend to foster the greatest interest.[56] Other challenges include limited guidelines on extrapolation of approved indications for biosimilars, the possibility of immunogenicity events in patients during testing, interchangeability with the originator drug, appropriate formulation and manufacturing of biosimilars, limited awareness of the efficacy and safety of biosimilars among health care providers, and potential political barriers. These issues are discussed in greater detail in subsequent paragraphs.

Selection of End Points

The choice of end points is paramount when designing studies of biosimilars. For biologics, the NCCN recommends using sensitive end points such as overall response rate (ORR), OS, and/or progression-free survival (PFS).[2] For biosimilars, end points should be relevant to the disease and sensitive enough to detect clinically relevant differences between the biosimilar and its reference drug.[28] The EMA and FDA recommend using end points that can facilitate detection of differences but are not influenced by patient- or disease-related factors.[28] According to EMA guidance on end point selection, a clinical end point that measures activity (eg, ORR) as a primary end point may be considered. Assessment of ORR at a certain time point or percentage change in tumor mass from baseline is also considered appropriate.[32] OS, the preferred efficacy end point in oncology, may not be suitable to establish biosimilarity, because it can be influenced by factors that are unrelated to the differences between a biosimilar and its reference product; also, OS as an end point would require conducting much larger trials with longer follow-up periods.[32]

It is important to validate the effectiveness of biosimilars not only through clinical trials but also in real-world settings. Although most regulatory authorities demand clinical trials that demonstrate safety and efficacy in a structured setting, reimbursement authorities may require data in real-world settings where patient selection is not restricted by strict inclusion and exclusion criteria.[57] Real-world studies with encouraging results can also help build clinicians' confidence in prescribing biosimilars.[58] Manufacturers realize the emerging importance of real-world data, leading to more studies of this type being conducted to complement clinical trials.[58]

Extrapolation of Approval to Other Indications

On the basis of data submitted for one indication, regulatory agencies generally determine whether extrapolation to all approved indications of the reference drug should be allowed. EMA guidelines state that if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.[37] Furthermore, manufacturers do not need to demonstrate biosimilarity again with changes in manufacturing steps, provided that marketing authorization has already been granted. In terms of procuring FDA approval, the 351(k) pathway is more appropriate when approval is desired for many indications at once; this pathway, however, requires a more rigorous level of clinical study. In contrast, the 351(a) pathway is faster, but approval is usually

granted for fewer indications.[59] Therefore, if the FDA requires rigorous clinical evidence for extrapolated indications in the 351(k) pathway, manufacturers may prefer the abbreviated 351(a) pathway. For example, tbo-filgrastim (Granix; Teva Pharmaceutical Industries, Petah Tikva, Israel) was filed through a 351(a) pathway and approved for one indication (neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy),[60] which was not the most desired indication for that product. Had tbo-filgrastim been filed through the 351(k) pathway, it potentially would have been eligible to gain extrapolation for all five indications for filgrastim.[59] Thus, it is important for manufacturers to have clear guidance on extrapolation of indications from the regulatory authorities to ensure appropriate filing.

In 2012, the Indian Department of Biotechnology laid out detailed guidelines and requirements for the development and approval of biosimilars for primary and extrapolated indications.[34] Several aspects of these guidelines are similar to those in the United States and European Union.[39] In Brazil, two pathways have been established to regulate the extrapolated prescription of biosimilars. In the individual pathway, the development process, dossier, quality issues, and requirements for clinical studies are reduced, but indications cannot be extrapolated. In contrast, extrapolations are allowed in the comparability pathway after satisfactory completion of rigorous phase I, II, and III clinical trials against the reference biologic.[1,10] When possible, clarity should be obtained on extrapolations at the time of launch. If physicians are not well informed of the nonpermitted extrapolations, they may unduly lose trust in the efficacy of the biosimilar, causing lower-than-expected adoption rates.

Immunogenicity

Biologics and biosimilars have the potential to induce antibody responses, which may result in hypersensitivity reactions and other adverse events (AEs) as well as decreased activity.[1] In particular, biosimilars with post-translational modifications are not exactly identical to reference biologics and can trigger an immune response.[36] Immunogenicity may be influenced by patient-, disease-, and/or product-related factors. Patient- and disease-related factors can be derived from original product data. Therefore, evaluations should focus on product-related factors, such as differences in structure between the biosimilar and reference medicine, impurities in preparation of the biosimilar, and changes in storage and/or distribution conditions of the biosimilar. Even seemingly small differences in these factors can affect immunogenicity and pose a risk to patients. Thus, appropriate clinical studies with comprehensive efficacy and safety end points are necessary for each biosimilar, especially because analytic or animal data cannot predict immune response in humans.[1,61]

Issues Related to Manufacturing

The consistent replication of biosimilar manufacturing and formulation processes is critical because even small alterations can have serious ramifications. For example, a minor change in the packaging process of a reformulation of epoetin alfa (Eprex; Janssen Pharmaceuticals) resulted in an increased rate of pure red-cell aplasia, prompting manufacturers to be more vigilant regarding any changes in formulations or manufacturing procedures.[62,63] The experience of the manufacturers in the field of biologics and the robustness of their production and supply chain abilities are important to ensure adequate supply of biosimilars over time. A lag in supply could lead to dose delays or reductions or result in patients switching to an alternate drug.[56]

Interchangeability

Interchangeability means that a biosimilar can be used as a substitute for the original drug without referring to the prescribing physician.[64] Given the sensitivity related to the manufacturing of biosimilars, their interchangeability is more complicated than the bioequivalence and interchangeability of generic drugs. The BPCI Act of 2009 authorizes the FDA to designate interchangeable status to a biosimilar with its reference drug after successful completion of specific studies.[38] These studies include analytic studies demonstrating similarity, animal studies including assessment of toxicity, and clinical studies including assessment of immunogenicity and PKs and PDs. To achieve interchangeable status, the BPCI Act further requires that the biosimilar and its reference use a similar mechanism of action and have the same route of administration, dosage form, strength, and indications, which should be previously approved for the reference drug. Finally, it should be ascertained that interchanging the original drug with its biosimilar does not increase risk in terms of safety or diminished efficacy.[38] FDA recommendations on interchangeability of biosimilars were released in January 2017. According to this guidance, the FDA expects that the sponsors will submit data and information showing that the proposed biosimilar can be expected to produce the same clinical results as the reference

product in all of the licensed conditions of use of the reference product in any given patient. This, however, may vary depending on the nature of the product under consideration.[65] Although these guidelines enlist a detailed and rigorous process for attaining interchangeable status, such status could help build the confidence of physicians in prescribing biosimilars.

Awareness Among Health Care Providers and Patients

In 2011, the NCCN conducted a survey among the attendees of its 16th annual conference in Hollywood, FL, to assess the awareness of biosimilars. The participants consisted of 277 health care providers, including physicians, nurses, pharmacists, and other practicing and nonpracticing clinicians.[2] Results indicated that more than half of the respondents were either not at all familiar (36%) or slightly familiar (19%) with recent developments regarding biosimilars; only 7% were extremely familiar. Overall interest in prescribing, dispensing, or administering biosimilars was high (27%) to moderate (35%); others expressed the need for more information before they could make a decision. The survey concluded that there was suboptimal knowledge of biosimilars and a need for greater awareness and education regarding biosimilars among health care providers. Another survey conducted among US physicians identified a strong need for evidence-based education about biosimilars for physicians across specialties.[66] Major knowledge gaps included a lack of proper understanding of the concept of totality of evidence, lack of clarity on permitted extrapolations, and unclear information on interchangeability and rules for pharmacy-level substitution of drugs. Pharmacists have also expressed low confidence in prescribing or interchanging biosimilars because of a lack of clear guidelines on naming conventions.[67] According to an online survey conducted among members of the Academy of Managed Care Pharmacy and the Hematology/Oncology Pharmacy Association, US pharmacists prefer the use of a naming convention for biosimilars that includes a nonproprietary proper name with a designated suffix, with the exact same nonproprietary name as the reference drug being more preferable.[67] These findings highlight the urgent need for establishing a proper naming convention for biosimilars to increase confidence in prescribing.

Likewise, awareness of biosimilars is also low among the patient population. A recent survey was conducted among patients, caregivers, patients involved in support or advocacy groups, and the general population based in either the United States or the European Union on their perceptions of biosimilar use.[68] Results revealed that across all groups, awareness of biosimilars was low, and only 6% of the general population reported some knowledge of biosimilars. Awareness was significantly high only among patients involved in support or advocacy groups (20% to 30%; $P < .05$). Gaps in knowledge about biosimilars, as identified by the survey, included safety, efficacy, and access. Limited awareness among providers and users could be a major reason for low adoption rates of biosimilars despite the availability of data on their clinical efficacy.

Potential Political Barriers?

There have been few political barriers to the development and accessibility of biosimilars.[69] A biosimilar manufacturer, while offering price reductions, may not be able to offer as complete a package as an innovator (eg, patient assistance program).[70] Furthermore, price competition alone may not be a sufficient offering, because the innovator drug manufacturer is likely to lower the price of the reference drug in response to the launch of a biosimilar.[69] It is also notable that the patent monopoly may be further strengthened by the provisions of agreements such as the Trans-Pacific Partnership .[71] The Trans-Pacific Partnership is a proposed trade deal between 12 Asia-Pacific countries, including the United States, that would expand and protect patent rights. This may have limitations in access to affordable health care.[72]

CASE STUDIES OF SPECIFIC BIOSIMILARS

A recent review by Jacobs et al[73] presented a grid that mapped the extent of similarity of various biosimilars and their reference drugs in the context of clinical, preclinical, or postmarketing studies. The observations emphasize the point that each study should be analyzed in the context of its setting and design. In the next few sections, we present experiences with a few select biosimilars that are most commonly prescribed during cancer treatment and a few other therapeutic areas.[2] With these case studies (presented in alphabetic order), we aim to provide a broad picture of the overall developmental landscape of these biosimilars in a concise manner.

Bevacizumab Biosimilars

Some of the bevacizumab biosimilars in late stages of development globally include ABP 215 (Amgen), BCD-021 (BIOCAD, Moscow,

Russia), Bevacirel (Reliance Life Sciences, Mumbai, India), BI 695502 (Boehringer Ingelheim, Ingelheim am Rhein, Germany), Cizumab (Hetero Drugs, Hyderabad, India), DRL_BZ (Dr Reddy's Laboratories; Clinical Trials Registry India identifier CTRI/2016/01/006481), PF-06439535 (Pfizer), and SB8 (Samsung Bioepis, Incheon, Republic of Korea).[74] Recent phase III results of a safety and efficacy study in adult patients with advanced non–small-cell lung cancer showed that the ORR (primary end point) after treatment with ABP 215 was within the prespecified margin compared with bevacizumab, demonstrating clinical equivalence of the two drugs. Safety and immunogenicity were comparable. Results of secondary end points were consistent with the primary findings and included risk difference of ORR, duration of response, and PFS.[61]

In a 2015 ASCO meeting, interim results were released from an ongoing phase III, multicenter, double-blind, randomized clinical trial comparing the efficacy of BCD-021 and paclitaxel plus carboplatin with Avastin and paclitaxel plus carboplatin in 138 patients with inoperable or advanced nonsquamous non–small-cell lung cancer .[75] The results showed no statistically significant differences between the two groups for the primary end point of ORR. Safety profiles were similar, and the biosimilar was concluded to be noninferior to Avastin. On the basis of these results, BCD-021 was approved for use in Russia in 2016.[76]

Darbepoetin Biosimilars

Several darbepoetin biosimilars are already in use in India[40] after the 2010 launch of Cresp (Dr Reddy's Laboratories), the first darbepoetin alfa biosimilar in the world. Cresp was approved in India for the treatment of anemia resulting from chronic kidney disease or cancer chemotherapy.[77] Darbepoetin biosimilars that are approved or actively being developed globally include Actorise (Cipla, Mumbai, India; Hetero Drugs), CKD-11101 (Chong Kun Dang Pharmaceutical, Seoul, Republic of Korea), DA-3880 (Dong-A ST, Seoul, Republic of Korea),[78] and Darbatitor (Torrent Pharmaceuticals, Gujarat, India).[79]

Filgrastim Biosimilars

The filgrastim biosimilar Zarxio (Sandoz) was approved in the European Union in 2009 and in the United States in 2015. The physicochemical properties and in vitro biologic activity of Zarxio were compared with those of Neupogen using a variety of assays. Results showed similar molecular structures, purity profiles, and equivalent biologic activity in terms of effect on cell proliferation.[80] Results of a randomized, double-blind, two-way crossover phase I study in healthy participants showed similar PKs and PDs and safety profiles between the two drugs.[81] Results of a double-blind, randomized phase III study evaluating Zarxio in 218 neutropenic patients receiving myelosuppressive chemotherapy showed no clinically meaningful differences in duration of severe neutropenia, incidence of febrile neutropenia, rate of hospitalization because of febrile neutropenia, incidence of infection, depth and time of absolute neutrophil count nadir, and time to absolute neutrophil count recovery. AE profiles were comparable between the two agents.[19] In 2013, Zarxio sales surpassed those of Neupogen in the European Union.[82]

Another filgrastim biosimilar, Grafeel (Dr Reddy's Laboratories), received regulatory approval in India in 2001. The EMA accepted the manufacturer's proposal that the clinically important difference between a biosimilar and its reference filgrastim was the difference of more than 1 day of severe neutropenia after myelosuppressive therapy.[83] Extrapolated approval for Grafeel was obtained for peripheral blood stem-cell mobilization and chronic, cyclic, or difficult-to-treat neutropenia. A pegylated version of Grafeel (Peg-Grafeel) was introduced by Dr Reddy's Laboratories in India in 2011 at a cost 25% lower than the price of the reference brand in India and 95% lower than the US price for pegfilgrastim, thereby increasing access to an affordable biosimilar for the treatment of neutropenia.[84]

Other filgrastim biosimilars that have been approved in various countries include Biograstim (CT Arzneimittel, Ulm, Germany), Filgrastim Hexal (Hexal), Grastofil (Apotex, North York, Ontario, Canada), MK-4214 (Merck, Kenilworth, NJ), Nivestim (Hospira, Lake Forest, IL), Ratiograstim (Ratiopharm, Ulm, Germany), and Tevagrastim (Teva Pharmaceutical Industries).[20,85-87] Many filgrastim biosimilars have been made available in India over the last 5 years by various pharmaceutical companies (Table 3).[87]

Rituximab Biosimilars

In 2007, the rituximab biosimilar Reditux (Dr Reddy's Laboratories) became the first monoclonal antibody biosimilar to be licensed in India.[40] It is one of the oldest rituximab biosimilars in use in the country for the treatment of non-Hodgkin lymphoma and rheumatoid arthritis. In a study conducted among 223 patients with diffuse large

B-cell lymphoma, it was observed that complete remission rates with the reference drug (MabThera; Roche) and Reditux were similar (75% and 82%, respectively; $P = .294$). There were no significant differences in toxicity, tumor response rates, PFS, and OS. The results of this retrospective analysis further revealed that there were no differences in infusion reaction rate and grade 3 to 4 neutropenia.[18] Most oncologists in India are now successfully using Reditux, leveraging the cost benefit it brings to patients.[18]

Some of the other rituximab biosimilars in various stages of development include AMG 798 (Amgen)[88]; CT-P10 (Celltrion, Incheon, Republic of Korea)[89]; GP2013 (Sandoz), with nonclinical assessments complete[90] and phase III trial completion expected in 2017[89]; MabionCD20 (Mabion, Konstantynów Łódzki, Poland), with phase III trial completion expected in 2016; MK-8808 (Merck)[89]; PF-05280586 (Pfizer), with nonclinical assessments complete[89,91] and phase III trial completion expected in 2016; and RTXM83 (mAbxience, Lugano, Switzerland).[92]

Trastuzumab Biosimilars

In 2013, the trastuzumab biosimilar Hertraz (Biocon-Mylan, Bangalore, India; alternative name, MYL-14010) was approved in India for the treatment of HER2-positive breast cancer based on a series of physiochemical and functional assays using Herceptin as the reference biologic.[93] Results confirmed similarities in molecular structure and biologic activity between the biosimilar and its reference.[94] Recently, Mylan (Amsterdam, the Netherlands) completed a double-blind, randomized safety and efficacy study (N = 500) comparing MYL-14010 with Herceptin.[95] In combination with taxane, MYL-14010 had no significant differences in efficacy compared with the reference as measured by ORR at week 24 (MYL-14010 plus taxane, 69.6%; Herceptin plus taxane, 64%). The ratio of ORR was 1.09; both 90% CI (0.974 to 1.211) and 95% CI (0.954 to 1.237) were within the predefined equivalence margins. Median PFS has not yet been reached (41 events for MYL-14010 *v* 48 events for Herceptin). Safety was comparable; serious AEs (primarily neutropenia related) occurred in 38% of those in the MYL-14010 group compared with 36% in the Herceptin group. These results suggest that the proposed trastuzumab biosimilar MYL-14010 could be a new treatment option for HER2-positive metastatic breast cancer.[95]

In 2014, a trastuzumab biosimilar called CT-P6 (Celltrion; alternative name, Herzuma) was approved in Korea for the treatment of early and advanced HER2-positive metastatic breast cancers and advanced metastatic stomach cancer, the same indications as its reference biologic, Herceptin.[96] Results of a double-blind, randomized phase I/IIb study of 174 women with HER2-positive breast cancer and an Eastern Cooperative Oncology Group score of 0 or 1 showed that CT-P6 and trastuzumab had similar PK profiles. CT-P6 was well tolerated, with a safety profile comparable to that of trastuzumab.[97] In a phase III trial, which enrolled 475 patients with breast cancer at 115 sites in 18 countries, safety and efficacy (ORR, median time to progression, and median time to response) of CT-P6 plus paclitaxel compared with trastuzumab plus paclitaxel were not significantly different. In fact, there were fewer infusion and hypersensitivity reactions with the biosimilar molecule (CT-P6 plus paclitaxel, 15.6%; trastuzumab plus paclitaxel, 26%).[21]

Other trastuzumab biosimilars in various stages of development include ABP 980 (Amgen), BCD-022 (BIOCAD; ClinicalTrials.gov identifier NCT01764022), DRL_TZ (Dr Reddy's Laboratories; Clinical Trials Registry India identifier CTRI/2015/08/006085), PF-05280014 (Pfizer), and SB3 (Samsung Bioepis), with phase III trials slated for completion in 2016, 2015, 2017, 2018, and 2016, respectively.[98] A phase III, randomized, double-blind, multicenter, active-controlled study assessing the safety and effectiveness of ABP 980 in comparison with its reference drug (Herceptin) recently met its primary end point; no clinically meaningful differences between ABP 980 and Herceptin were identified.[99] In this study, a total of 725 women with HER2-positive early breast cancer were randomly assigned to receive either ABP 980 or Herceptin.[100] Safety profile and immunogenicity of the two drugs were comparable. The study is in its late stages, and the final results are expected in the near future.[100]

In conclusion, the universal demand for affordable, effective cancer treatments and greater access to biopharmaceuticals is propelling the rapid development of biosimilars. Increasing availability of biosimilars will enhance treatment options, improve patient access, and potentially stimulate price competition with reference medicines. Over the next few years, the global biosimilars market is projected to grow at a compound annual growth rate of nearly 50%.[101] Thus, biosimilars have the potential to revolutionize biologic therapies for cancer and other diseases. Clinical experiences with biosimilars have been promising thus far. However, greater education of

health care providers regarding appropriate use of biosimilars is needed. Coordinated interplay among various stakeholders, including patients, health care providers, drug manufacturers, payers, and regulatory agencies, can ensure that the promise of biosimilars is fully realized.

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