HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Rationale, Opportunities, and Reality of Biosimilar Medications

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Biologic therapies for cancer and other disorders contribute to improved outcomes for many patients but also account for a large proportion of health care expenditures. Opportunities for cost containment may emerge as the patents on originator products expire and highly similar agents known as biosimilar medications reach the clinic. Biosimilar formulations of myeloid growth factors that are used to reduce chemotherapy toxicity are already available, and the recent approval of what is likely to be the first wave of biosimilar cancer therapies will provide treatment options that, if accepted by providers and patients, may help constrain health care spending. In this article, we summarize the current status of biosimilar agents in the United States. Although we focus on oncology, the regulatory issues and challenges related to naming, labeling, and postmarketing surveillance, as well as challenges related to implementation in practice (including compliance with guidelines, coverage, and reimbursement), are relevant across all medical disciplines. Considerable professional and patient education will be important, along with rational and sustainable policies, to ensure the appropriate and effective use of biosimilar medications in clinical practice.

INTRODUCTION

THE OPPORTUNITIES

The continuing rise in health care costs, highlighted by the rapid increase in the price of cancer drugs in the United States, has prompted a concerted effort to find new strategies to contain costs while improving access to safe and effective treatments. Nowhere is this more apparent than with biologic therapies, which represent a large proportion of the new anticancer agents introduced over the past two decades. Several of these drugs now face patent expiration and competition from a new class of agents known as biosimilars. A biosimilar is a biologic agent that is not chemically identical, but is highly similar, to an approved reference biologic agent, with no meaningful differences in efficacy, safety, and purity.[1,2] The biologic oncology products that are expected to lose patent protection by 2020 account for more than $20 billion in global annual spending, and biosimilars are anticipated to assume the majority of the market share for a number of these drugs.[3] Although the effect of biosimilars on health care costs is not yet clear, a recent analysis from the RAND Corporation estimates that the introduction of biosimilars could potentially reduce direct spending by $54 billion between 2017 and 2026.[4]

THE CHALLENGES

The Food and Drug Administration (FDA) has so far approved nine biosimilar products, including a biosimilar formulation of a myeloid growth factor that is used to reduce the toxicity of cancer chemotherapy (filgrastim-sndz as an alternative to Neupogen [Amgen]) and two biosimilar products for the treatment of cancer (bevacizumab-awwb as an alternative to Avastin [Genentech] and trastuzumab-dkst as an alternative to Herceptin [Genentech]). However, challenges remain concerning the acceptance of biosimilars by physicians and patients in the United States. Their overall effect on health care costs will be heavily influenced by provider, payer, and patient understanding of their safety and efficacy.[5-7] The regulatory process for approval of biosimilars is based largely on preclinical studies and deemphasizes the need for large phase 3 clinical trials.[1] Therefore, clinician confidence in the usefulness of these products will depend less on large randomized studies than on preclinical and pharmacologic data, along with clinical experience. Currently, confusion and uncertainty exist about the naming and labeling of biosimilars and their ap-

Table 1. ASCO Statement on the Use of Biosimilars in Oncology.*

Area of Guidance	Comment
Naming, labeling, and other regulatory considerations	Product naming and labeling of biosimilars, when considered together, will help ensure that clinicians and pharmacists have all the necessary information to establish confidence that they are using their chosen therapy as intended.
Safety and efficacy of biosimilars	Sustained development of postmarketing evidence is necessary to enhance patient and provider confidence in biosimilars and to supplement the evidence that supports the safe and effective use of biosimilar products.
Interchangeability, switching, and substitution	The ability of oncologists and patients to decide which available biologic product will provide the best available treatment is key to providing high-quality, high-value care. Interchangeability of a product is determined at the federal level after FDA review; however, substitution will be regulated at the state level. As individual states work to regulate the use of biosimilars, oncologists and patients must be aware of regulations, authorities, and responsibilities that may affect their treatment choices.
Value of biosimilars	Biosimilars provide an opportunity for obtaining desired outcomes and managing the cost of care for patients with cancer at the same time. Coverage and reimbursement policies vary by payer, patient, and clinical setting.
Prescriber and patient education	Ongoing education to providers is critical to promote the use of biosimilars and to inform clinicians regarding the use of biosimilars in a medically appropriate and cost-effective way. The provision of patient education about biosimilars by a knowledgeable health professional is also important. Public awareness and education and the use of standardized, publicly available materials from professional societies, government sources, and patient advocacy groups will help ensure understanding of biosimilar products.

* To provide education and guidance about biosimilars to clinicians caring for patients with cancer, the American Society of Clinical Oncology (ASCO) recently issued a statement addressing the assessment of safety and efficacy of biosimilars and their integration into clinical practice.[9] FDA denotes Food and Drug Administration.

propriate integration into clinical practice guidelines, as well as about coverage and reimbursement policies. In addition, concepts such as extrapolation, switching or automatic substitution, and interchangeability are new to most clinicians.[8] Minor modifications in manufacturing, processing, and packaging may result in lot-to-lot differences in both biosimilars and originator products, which could potentially lead to a small but real risk of differences in immunogenicity and adverse-event profiles appearing over time. Therefore, ongoing postapproval surveillance will be essential to track the effectiveness, safety, and usefulness of all therapeutic proteins, including biosimilars, as they are deployed in clinical practice.

To provide education and guidance about biosimilars to clinicians caring for patients with cancer, the American Society of Clinical Oncology (ASCO) recently issued a statement addressing the assessment of safety and efficacy of biosimilars and their integration into clinical practice (Table 1).[9] The ASCO statement comments on naming, labeling, and other regulatory considerations; safety and efficacy; interchangeability, switching, and substitution; and the economic effect of biosimilars. The statement highlights the need for ongoing professional and patient education to establish confidence in the safety and efficacy of biosimilars as their availability increases. Continued generation of evidence will require innovative and coordinated efforts across agencies, organizations, and institutions and will undoubtedly invoke emerging big-data capabilities.

MANUFACTURING AND REGULATION

MANUFACTURING OF BIOSIMILAR PRODUCTS

Therapeutic proteins including cytokines (e.g., epoetin alfa) and monoclonal antibodies (e.g., bevacizumab) are created by biologic processes in living cellular systems rather than through stepwise chemical synthesis. A biosimilar must have amino acid sequences that are the same as those in the reference brand-name drug but may have minor differences due to post-translational protein modifications (e.g., alterations to C or N terminals), glycosylation (addition of sugar residues to amino acids bearing amino or hydroxyl groups), or formulation (e.g., use of different excipients). Sponsors are required to provide "sufficient data and information demonstrating that the differences are not clinically meaningful and the pro-

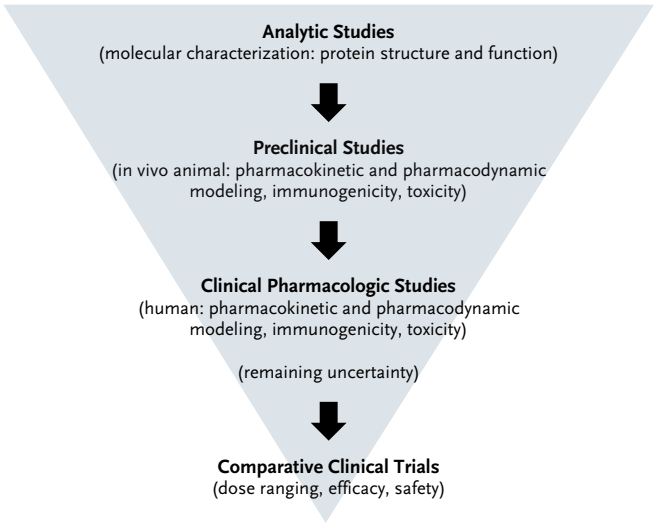

Figure 1. Regulatory and Approval Pathway for Biosimilars in the United States.

A biosimilar is a biologic agent that is not chemically identical, but is highly similar, to an approved reference biologic agent, with no meaningful differences in efficacy, safety, and purity. Preclinical investigation includes analytic studies of protein structure and function; assessment of activity and toxicity in animal models; and pharmacokinetic, pharmacodynamic, and immunogenicity studies. Clinical confirmation of biosimilarity is based on pharmacokinetic and pharmacodynamic studies and on studies of immunogenicity and other toxicities, with further confirmation of safety and efficacy in a clinical trial, if necessary, to resolve any uncertainty about product performance. The totality of the evidence is evaluated at each step to determine whether further studies are needed.[10,13,14] If uncertainty remains, comparative clinical dose ranging, efficacy, and safety studies may be required.[12]

posed product otherwise meets the statutory criteria for biosimilarity."[10] Manufacturing of a biosimilar begins with the selection of a unique cell line for transfer of a gene and vector to produce the protein of interest. This approach can yield differences in protein folding and structure, which may, in theory, lead to changes in clinical pharmacologic and immunogenic properties. The complexity of the production of biologic therapies — including both originator products and biosimilars — that involves the use of living cells leads to inherent differences in biologic products. Therefore, it is essentially impossible to create a therapeutic protein that is identical or fully equivalent to a reference product, as is possible with generic drugs. Indeed, even batches of the same reference product that are produced with the use of the same cell line may be dissimilar.[11] Regulatory agencies expect companies to assess differences between the biosimilar and the reference product at each manufacturing step for potential effects on safety and efficacy and to eliminate residual uncertainty through preclinical studies and alterations in manufacturing processes, if needed. Preclinical investigation typically includes analytic studies of protein structure and function; assessment of activity and toxicity in animal models; and pharmacokinetic, pharmacodynamic, and immunogenicity studies. After bulk production of the biosimilar, a final comparison with the reference product is made to assess structure, biologic properties (binding, cross-reactivity, immunogenicity, and complement fixation), and stability under various conditions.[12]

REGULATORY APPROVAL

Regulatory review of biosimilars differs from that of generic drugs or originator biologic agents.[10,13,14] Although molecular characterization and preclinical data are essential, the primary data to support marketing approval for originator biologic agents are derived from clinical trials. In contrast, the regulatory review of biosimilars is far more focused on molecular characterization and preclinical studies. Clinical confirmation of biosimilarity is based primarily on pharmacokinetic and pharmacodynamic studies, as well as on studies of immunogenicity and other toxicities, with further confirmation of safety and efficacy in a clinical trial, if necessary, to resolve any remaining uncertainty about product performance. The FDA evaluates the totality of the evidence at each step to determine whether further studies are needed to eliminate any uncertainty regarding the similarity of the biologic product and the biosimilar (Fig. 1).[10,13,14] If uncertainty remains, comparative clinical dose-ranging, efficacy, and safety studies may be required.[12] Although the underlying amino acid sequence and mechanism of action will be the same in the biosimilar and the reference biologic product, there may be differences in the host cell line, the protein structure, various inactive ingredients, and the overall manufacturing process. Definitions relevant to the approval pathway of biosimilars are summarized in Table 2.[15]

In addition to extensive manufacturing and preclinical data, companies must provide data showing pharmacokinetic similarity to the reference product; such data are typically obtained from a single-dose, crossover trial. A single comparative

Table 2. FDA Definitions and Terminology Pertinent to Biosimilars.

Term	Definition and Application
Generic	A generic medication is a drug product that is the same as a brand or reference-listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use. The term generic is classically applied to small molecules and agents that undergo a multistep chemical synthesis. Approval is based on pharmaceutical equivalence and human bioequivalence to a branded agent. Biosimilars do not meet this definition because of differing manufacturing methods.[15]
Reference product	A reference product is an approved drug product that is compared with the new generic or biosimilar versions to show they are bioequivalent or biosimilar.[15]
Biosimilarity	Biosimilarity describes a biologic product that "is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and has "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."[10] To show biosimilarity, a great weight of evidence is placed on chemical manufacturing and controls because of the complexity of protein production; often 50% or more of the data in applications for approval of biosimilar products refer to manufacturing processes.
Interchangeability	An interchangeable biosimilar can be expected to produce the same clinical results as the reference product in any given patient, and, if given more than once, data show that switching between products presents no greater safety or efficacy risk than continuous treatment with the reference product. FDA designation of a biosimilar product as interchangeable effectively means that clinicians could substitute the biosimilar at any point during therapy with the greatest degree of confidence.

clinical study must also be performed and must show no meaningful differences in safety and efficacy between the biosimilar product and the reference product. Applications for regulatory approval of biosimilars are not required to include repeat trials across indications, and once approved, biosimilar drugs may be granted labeling that is identical to that of the reference product for clinical use — a strong incentive for the development of biosimilars.

The European Medicines Agency (EMA) has approved 40 biosimilar products at the time of this writing, with 15 available for use in oncology (Tables 3 and 4).[15,16] In the United States, biosimilar oncology agents have been approved for both supportive care and anticancer therapy, and more agents (biosimilars for cetuximab and rituximab) are now in the late stages of development.[17] Regulatory approval does not necessarily lead to commercial availability, because manufacturers of the originator drug often use patent infringement litigation to delay marketing of the biosimilar.[18] Another delay tactic used by the patent-holding company is to actively prevent the sale of the originator drug to the biosimilar company in clinically sufficient quantities to enable comparative clinical testing — a practice that may soon be overcome by legislation. Nevertheless, multiple companies, including those that developed the originator products, are pursuing the development of biosimilars for use in oncology, immunology, rheumatology, and other therapeutic areas (Table 5).[19-23]

NAMING, LABELING, AND POSTMARKETING SURVEILLANCE

Nonproprietary names with a meaningless four-letter suffix are assigned to biosimilar products to allow the identification of unique products for prescribing and postmarketing safety monitoring. Labels for biosimilars describe comparisons with the reference product, and clinicians can therefore see the source of data and understand the therapeutic profile of the biosimilar and the reference product side by side. Pharmacovigilance reporting is critical for biosimilars, because differences in manufacturing may result in differences in safety, such as in immunogenicity, when agents are used in larger and more heterogeneous populations.[24]

INTERCHANGEABILITY

An interchangeable biosimilar can be expected to produce the same clinical results as the reference product when substituted for the reference product at any point in therapy and presents no greater safety risk than continuous treatment with the reference product. To date, no biosimilar has been approved in the United States as a fully interchangeable product. The value of this desig-

Table 3. Biosimilar Agents Approved for Use in the European Union.*

Molecule	Biosimilar Agent by Trade Name (Manufacturer)	Year Approved
Nononcology		
Somatropin	Omnitrope (Sandoz)	2006
	Valtropin (BioPartners)	2006, withdrawn 2012
Epoetin alfa	Abseamed (Medice Arzneimittel Putter)	2007
	Binocrit (Sandoz)	2007
	Epoetin alfa Hexal (Hexal)	2007
Epoetin zeta	Silapo (Stada Arzneimittel)	2007
	Retacrit (Hospira)	2007
Infliximab	Inflectra (Hospira)	2013
	Remsima (Celltrion)	2013
	Flixabi (Samsung Bioepis)	2016
Follitropin alfa	Ovaleap (Teva)	2013
	Bemfola (Finox Biotech)	2014
Insulin glargine	Abasaglar (Eli Lilly/Boehringer Ingelheim)	2014
	Lusduna (Merck)	2017
	Semglee (Mylan)	CHMP positive opinion 2018
Insulin lispro	Insulin lispro Sanofi (Sanofi-Aventis)	CHMP positive opinion 2017
Enoxaparin	Inhixa (Techdow Europe)	2016
	Thorinane (Pharmathen)	2016
Etanercept	Benepali (Samsung Bioepis)	2016
	Erelzi (Sandoz)	2017
Teriparatide	Movymia (Stada Arzneimittel)	2017
	Terrosa (Gedeon Richter)	2017
Adalimumab	Amgevita (Amgen)	2017
	Solymbic (Amgen)	2017
	Imraldi (Samsung Bioepis)	2017
	Cyltezo (Boehringer Ingelheim)	CHMP positive opinion 2017
Oncology		
Filgrastim	Biograstim (CT Arzneimittel)	2008, withdrawn 2016
	Ratiograstim (Ratiopharm)	2008
	Tevagrastim (Teva)	2008
	Filgrastim Hexal (Hexal)	2009
	Zarzio (Sandoz)	2009
	Nivestim (Hospira)	2010
	Grastofil (Apotex)	2013
	Accofil (Accord Healthcare)	2104
Rituximab	Truxima (Celltrion)	2017
	Riximyo (Sandoz)	CHMP positive opinion 2017
	Rixathon (Sandoz)	2017
	Blitzima (Celltrion)	2017
	Ritemvia (Celltrion)	2017
	Rituzena (Celltrion)	2017
Trastuzumab	Ontruzant (Samsung Bioepis)	2017
	Herzuma (Celltrion Healthcare)	CHMP positive opinion 2017
Bevacizumab	Mvasi (Amgen)	2018

* The table shows the biosimilar agents that were approved by the European Medicines Agency for use in the European Union.[16] CHMP denotes Committee for Medicinal Products for Human Use of the European Medicines Agency.

nation is yet to be determined, and nonproprietary product-naming conventions for interchangeable biosimilars that are distinct from those not deemed interchangeable is under consideration.[25] If approved as an interchangeable biosimilar, state-specific laws may allow pharmacists to substitute a biosimilar that has been shown to be interchangeable for a reference product without

Table 4. Biosimilar Agents Approved for Use in the United States.*

Reference Product by Generic Name (Trade Name, Manufacturer)	Biosimilar Agent by Nonproprietary Name (Trade Name, Manufacturer)	Year Approved	Year Marketed
Nononcology			
Infliximab (Remicade, Janssen Biotech)	Infliximab-dyyb (Inflectra, Celltrion/Pfizer)	2016	2016
	Infliximab-abda (Renflexis, Samsung Bioepis)	2017	2017
	Infliximab-qbtx (Ixifi, Pfizer)	2017	Not available
Etanercept (Enbrel, Amgen)	Etanercept-szzs (Erelzi, Sandoz)	2016	Not available
Adalimumab (Humira, AbbVie)	Adalimumab-atto (Amjevita, Amgen)	2016	Not available
	Adalimumab-adbm (Cyltezo, Boehringer Ingelheim)	2017	Not available
Oncology			
Filgrastim (Neupogen, Amgen)	Filgrastim-sndz (Zarxio, Sandoz)	2015	2015
Bevacizumab (Avastin, Genentech)	Bevacizumab-awwb (Mvasi, Amgen)	2017	Not available
Trastuzumab (Herceptin, Genentech)	Trastuzumab-dkst (Ogivri, Mylan/Biocon)	2017	Not available

* No biosimilar agent approved in the United States has been designated as an interchangeable product.

consulting prescribers, as may be done with generic drugs in current practice. It is likely that a designation of interchangeable will become more relevant as multiple biosimilars are approved for a specific reference product and manufacturers look for competitive advantages.

CLINICAL CHALLENGES AND THE PATH FORWARD

Biosimilars are entering the U.S. market in increasing numbers and will be assimilated into therapeutic regimens by several medical specialties. The international experience with biosimilars thus far has shown improved patient access and reduced costs.[26] In the United States, however, the use of biosimilars in clinical practice may face challenges stemming from limited provider and patient education, uncertain compliance with postmarketing surveillance requirements, and variable reimbursement and coverage policies.[5] The savings in direct expenditures associated with use of biosimilars will probably depend on payment arrangements, regulatory policies and guidance, and patient and prescriber acceptance, among other issues.[4] Therefore, there are opportunities to deploy strategies that will ensure that biosimilars are incorporated into the delivery of high-quality, high-value care.

EDUCATION

Education and training must be available to the clinical care team and patients to build confidence in biosimilars. Professional societies and government agencies can play an important role by providing a broad range of educational materials to all stakeholders. For providers, education can be incorporated into professional society meetings, clinical practice guidelines, educational webinars, and social media updates. For patients, multilingual materials should be available and written at an average reading level to supplement education provided by clinical staff. ASCO has developed Web-based educational materials for both professionals and patients.[27] Because patients with cancer may have multiple providers, education is needed for primary care physicians and other providers involved in cancer care.

SAFETY AND POSTMARKETING SURVEILLANCE

In light of the limited clinical studies required for regulatory approval, the FDA and clinical community will rely heavily on postmarketing evidence to confirm the overall safety and efficacy of biosimilars. However, many clinicians consider the current system for postmarketing reporting of adverse events to be cumbersome and opt out of this process because of time and resource constraints. The poor interoperability of electronic health records and the increasing administrative burden on physicians contribute to the challenges of collecting postmarketing data. Currently, various systems for the collection of data on real-world clinical outcomes exist, including the FDA Sentinel Initiative, postmarketing safety registries, and integrated health information systems such as the

Table 5. Biosimilar Products in Development in the United States.*

Reference Product by Generic Name	Mechanism of Action	U.S. Patent Expiration	Current Status
Filgrastim	Colony-stimulating factor	2013	Product developed by Adello accepted for FDA review in September 2017
Pegfilgrastim	Long-acting colony-stimulating factor	2015	Two agents accepted for FDA review: MYL1401H (Mylan/Biocon) and CHS-1701 (Coherus) MYL1401H: FDA issued complete response letter CHS-1701: rejected by FDA in June 2017
Cetuximab	EGFR receptor inhibition	2016	ABP494 (Actavis/Amgen): remains in preclinical development
Rituximab	CD20 receptor inhibition	2016	ABP798 (Actavis/Amgen): phase 3 trial in non-Hodgkin's lymphoma expected to be completed in late 2018 CT-P10 (Celltrion/Teva): accepted for FDA review in June 2017 GP2013 (Sandoz): accepted for FDA review in September 2017
Adalimumab	Binds soluble TNF	2017	CHS-1420 (Coherus): phase 3 trial completed in January 2017 ONS-3010 (Oncobiologics/Viropro): phase 3 trial to start in 2018 PF-06410293 (Pfizer): phase 3 trial ongoing
Denosumab	Binds RANK ligand	2017	ONS-4010 (Oncobiologics): preclinical work ongoing
Infliximab	TNF receptor inhibition	2018	ABP710 (Amgen): in development NI-071 (Nichi-Iko): phase 3 trial expected to be completed in February 2019
Bevacizumab	Binds soluble VEGF	2019	ONS-1045 (Oncobiologics/Viropro): phase 3 trial to start in 2018 PF-06439535 (Pfizer): phase 3 trial in lung cancer started in February 2015 SB8 (Samsung Bioepis/Merck): phase 3 in lung cancer ongoing
Trastuzumab	HER2 receptor inhibition	2019	CT-P6 (Celltrion/Teva): application submitted to FDA in July 2017 ONS-1050 (Oncobiologics/Viropro): phase 1 trial to start in 2018 PF-05280014 (Pfizer): application submitted to FDA in September 2017
Ranibizumab	Binds soluble VEGF	2020	CHS-3351 (Coherus): preclinical work ongoing PF852 (Hospira/Pfizer): phase 2 trial in age-related macular degeneration ongoing

* The table shows the biosimilar agents that are under development in the United States.[19-23] EGFR denotes epidermal growth factor receptor, HER2 human epidermal growth factor receptor 2, RANK receptor activator of nuclear factor κB, TNF tumor necrosis factor, and VEGF vascular endothelial growth factor.

ASCO CancerLinQ; these systems have the potential to contribute important information about biosimilar use, safety, and effectiveness.

REIMBURSEMENT, COVERAGE, AND COST

The Quality Payment Program, established under the Medicare Access and Children's Health Insurance Program Reauthorization Act, places pressure on providers and institutions to provide high-quality care that also delivers value to the health care system. Biosimilars have the potential to contribute to this goal. The Centers for Medicare and Medicaid Services has determined that all newly approved biosimilars that have a common reference product will be coded separately and reimbursed at the current rate of the average sales price (ASP) plus 6% of the ASP of the originator reference product minus any mandated sequester adjustment. The Medicaid program views biosimilars as "single source," which results in dif-

ferent reimbursement rates for each biosimilar. In contrast, under the Medicare Part D benefit, biosimilars are exempt from the Medicare Coverage Gap Discount Program, which requires manufacturers to provide a 50% discount on brand-name drugs and brand-name biologic drugs. As a result of this coverage gap, seniors and persons with disabilities will pay higher out-of-pocket costs for biosimilars than for competing reference biologic drugs. To close this gap, a legislative solution will be necessary to modify the definition of "applicable drugs" to include biosimilars. Otherwise, the cost-saving opportunity provided by the introduction of biosimilars may be lost entirely, and their use may be greatly diminished.

SUSTAINABILITY

In providing the best available care to patients, clinicians and institutions have many financial pressures, such as those involving policy coverage determinations, practices by pharmacy benefit managers, drug rebates, and the congressionally directed federal 340B drug discount program.[28,29] Because it is unclear how these factors will affect the uptake of biosimilars, overall cost, or physician prescribing authority, they must be monitored to ensure fair and transparent use. In order to develop successful strategies and best-practice guidelines to ensure patient access to these agents, it will be critical to better understand why and when biologic agents, including biosimilars, are used in practice.[30]

CASE EXAMPLES: FILGRASTIM-SNDZ AND TRASTUZUMAB-DKST

To gain FDA approval, the biosimilar drug filgrastim-sndz had to show bioequivalence to the reference originator drug filgrastim through chemical evaluation and clinical testing in trials with prespecified pharmacologic and clinical end points. First, a randomized, double-blind, two-way crossover, single-dose (10 μg per kilogram of body weight administered subcutaneously) pharmacokinetic and safety study involving 26 healthy volunteers was performed to compare the biosimilar with the reference originator product filgrastim.[31] Subsequently, a phase 3, randomized, double-blind, four-group comparative trial was conducted that included 218 patients with breast cancer who received 6 cycles of adjuvant or neoadjuvant chemotherapy. This trial showed clinical equivalence with respect to the primary end point of duration of severe neutropenia.[32] Although filgrastim-sndz (Zarxio, Novartis) was approved by the FDA in March 2015, it was not commercially available until September 2015 because of patent infringement challenges.[33] Once available, Zarxio took 4 months to gain 24% of the market at a price that was 15% lower at launch than that of the originator drug Neupogen (Amgen).[34,35] Currently, a 300-μg vial of Neupogen costs $377.80, and a 300-$\mu$g vial of Zarxio costs $330.79; the corresponding costs for 480-μg vials are $601.60 and $526.78.[36]

The development and approval of trastuzumab-dkst followed a similar path. A prospective, randomized equivalence trial involving 458 patients with human epidermal growth factor receptor 2–positive metastatic breast cancer compared the biosimilar drug trastuzumab-dkst with the reference originator drug trastuzumab (Herceptin, Genentech); both treatments were combined with taxane chemotherapy.[21] The primary efficacy end point of overall response rate at week 24 was derived from a meta-analysis of previously conducted randomized trials of trastuzumab plus chemotherapy. A two-sided 95% confidence interval for the difference in the overall response rates at week 24 was calculated, and equivalence was declared if the confidence interval was completely within the equivalence range.

CONCLUSIONS

The introduction of therapeutic proteins has revolutionized the practice of clinical medicine. At the same time, these biologic agents have contributed considerably to the rapid rise in health care expenditures. As patent exclusivity expires on these products, the opportunity to favorably bend the cost curve through the development of competing biosimilars has now emerged. At the same time, practitioners must rely on more limited clinical safety and efficacy data and must be educated regarding novel naming and labeling and new concepts such as interchangeability and switching; in addition, there is uncertainty about coverage and reimbursement and an even greater need for postmarketing surveillance. Nevertheless, the potential for biosimilars to mitigate rising health care costs while improving access to highly effective therapies provides a true opportunity to

reduce disparities in access to care and limit the financial burden of new treatments for cancer and other major illnesses. It is essential that professional organizations provide educational programs about biosimilars to inform the medical community of the opportunities and the challenges that these new agents provide for our patients now and in the years to come.

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1. Dougherty MK, Zineh I, Christl L. Perspectives on the current state of the biosimilar regulatory pathway in the United States. Clin Pharmacol Ther 2018;103:36-8.
2. Farhat F, Torres A, Park W, et al. The concept of biosimilars: from characterization to evolution — a narrative review. Oncologist 2018;23:346-52.
3. IMS Health. The impact of biosimilar competition. London: QuintilesIMS, June 2016 (https://www.scribd.com/document/349757084/IMS-Impact-of-Biosimilar-Competition-2016).
4. Mulcahy AW, Hlavka JP, Case SR. Biosimilar cost savings in the United States: initial experience and future potential. Santa Monica, CA: RAND, 2017.
5. Hirsch BR, Lyman GH. Will biosimilars gain momentum? J Natl Compr Canc Netw 2013;11:1291-7.
6. Hirsch BR, Lyman GH. Biosimilars: a cure to the U.S. health care cost conundrum? Blood Rev 2014;28:263-8.
7. Hakim A, Ross JS. Obstacles to the adoption of biosimilars for chronic diseases. JAMA 2017;317:2163-4.
8. Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. Adv Ther 2017;33:2160-72.
9. Lyman GH, Balaban E, Diaz M, et al. American Society of Clinical Oncology statement: biosimilars in oncology. J Clin Oncol 2018;36:1260-5.
10. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. Silver Spring, MD: Food and Drug Administration, April 2015 (https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf).
11. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol 2011;29:310-2.
12. Markus R, Liu J, Ramchandani M, Landa D, Born T, Kaur P. Developing the totality of evidence for biosimilars: regulatory considerations and building confidence for the healthcare community. BioDrugs 2017;31:175-87.
13. Yang L. Drug development overview — FDA: basic research to clinical use. Silver Spring, MD: Food and Drug Administration, June 12, 2012.
14. Olech E. Biosimilars: rationale and current regulatory landscape. Semin Arthritis Rheum 2016;45:Suppl:S1-S10.
15. Drugs@FDA glossary. Silver Spring, MD: Food and Drug Administration (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page).
16. Biosimilars approved in Europe. Generics and Biosimilars Initiative. February 2, 2018 (http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe).
17. Harvey RD. Science of biosimilars. J Oncol Pract 2017;13(9):Suppl:17s-23s.
18. Frank RG. Friction in the path to use of biosimilar drugs. N Engl J Med 2018;378:791-3.
19. Cuello HA, Segatori VI, Alberto M, Pesce A, Alonso DF, Gabri MR. Comparability of antibody-mediated cell killing activity between a proposed biosimilar RTXM83 and the originator rituximab. BioDrugs 2016;30:225-31.
20. Generics and Biosimilars Initiative (http://www.gabionline.net/).
21. Rugo HS, Barve A, Waller CF, et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-positive metastatic breast cancer: a randomized clinical trial. JAMA 2017;317:37-47.
22. Rugo HS, Linton KM, Cervi P, Rosenberg JA, Jacobs I. A clinician's guide to biosimilars in oncology. Cancer Treat Rev 2016;46:73-9.
23. Stevenson JG, Popovian R, Jacobs I, Hurst S, Shane LG. Biosimilars: practical considerations for pharmacists. Ann Pharmacother 2017;51:590-602.
24. Macdougall IC, Roger SD, de Francisco A, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: new insights. Kidney Int 2012;81:727-32.
25. Nonproprietary naming of biological products: guidance for industry. Silver Spring, MD: Food and Drug Administration, January 2017 (https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf).
26. The impact of biosimilar competition in Europe. London: QuintilesIMS, May 2017 (http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf).
27. ASCO in Action: news, advocacy, and analysis on cancer policy. Alexandria, VA: American Society of Clinical Oncology (https://www.asco.org/advocacy-policy/asco-in-action).
28. American Society of Clinical Oncology. The state of cancer care in America, 2017: a report by the American Society of Clinical Oncology. J Oncol Pract 2017;13(4):e353-e394.
29. Desai S, McWilliams JM. Consequences of the 340B Drug Pricing Program. N Engl J Med 2018;378:539-48.
30. Nabhan C, Feinberg BA. Behavioral economics and the future of biosimilars. J Natl Compr Canc Netw 2017;15:1449-51.
31. Sörgel F, Schwebig A, Holzmann J, Prasch S, Singh P, Kinzig M. Comparability of biosimilar filgrastim with originator filgrastim: protein characterization, pharmacodynamics, and pharmacokinetics. BioDrugs 2015;29:123-31.
32. Blackwell K, Semiglazov V, Krasnozhon D, et al. Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol 2015;26:1948-53.
33. McCaffrey K. Amgen, Sandoz argue biosimilar patent case to the Supreme Court. MM&M. April 27, 2017 (https://www.mmm-online.com/legalregulatory/amgn-nvs-biosimilar-supreme-court-amgen-novartis-zarxio/article/653227/).
34. Blank C. How new biosimilars will impact the market. Drug Topic. February 15, 2017 (http://drugtopics.modernmedicine.com/drug-topics/news/how-new-biosimilars-will-impact-market).
35. Hirschler B, Shields M. Novartis launches first U.S. biosimilar drug at 15 percent discount. Reuters. September 3, 2015 (https://www.reuters.com/article/us-novartis-drug/novartis-launches-first-u-s-biosimilar-drug-at-15-percent-discount-idUSKCN0R30C220150903).
36. Filgrastim (including biosimilars of filgrastim): drug information. Waltham, MA: UpToDate, 2018.

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