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Biosimilars in Oncology in the United States
A Review

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IMPORTANCE Biosimilars are biological medicines that contain a highly similar version of the active substance of an already approved biologic reference product. The availability of biosimilars might provide an opportunity to lower health care expenditures as a result of the inherent price competition with their reference product. Understanding how biosimilar cancer drugs are regulated, approved, and paid for, as well as their impact in a value-based care environment, is essential for physicians and other stakeholders in oncology.

OBSERVATIONS Important structural and regulatory differences exist between biosimilar and generic medications. Minor differences in clinically inactive components with no clinically meaningful differences between biosimilars and their reference biologic are allowed. A biosimilar uses the same mechanism of action as the reference biologic, and its condition of use is the same as the approved indication, although extrapolation is permitted across indications under regulatory guidance. A biosimilar has to have a similar route of administration, dosage, and strength as the reference biologic. As patent expiration of multiple cancer biologics will occur in the next few years, more biosimilars might enter the market. Whether the approval and use of biosmilars as replacements for these heavily prescribed reference biologics will ultimately lead to cost savings is unknown and requires longer follow-up. Two biosimilars with an oncology supportive care indication are currently approved in the United States; both are myeloid growth factors.

CONCLUSIONS AND RELEVANCE The financial impact of generic drug competition can be dramatic, but significant differences in regulatory and development processes between generics and biosimilars limit such comparisons and likely present significant challenges for biosimilar approval and adoption in the US market. However, a value-based care environment and their cost-savings potential make biosimilars an attractive option for the therapeutic arsenal. Oncologists' understanding of biosimilars is critical to moving forward.

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Supplemental content

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In 1984, the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) became law, allowing the US Food and Drug Administration (FDA) to approve applications for generic versions of brand-name drugs without repeating the research that proved the brand drug's safety and efficacy.[1] The act was conceived in an era when drugs were chemically synthesized and generic versions were structurally identical to their reference brands. However, ongoing innovation would soon challenge this definition of generic drugs. In 1982, Eli Lilly developed a method using bacteria to synthesize human insulin via recombinant DNA technology.[2] The result of this scientific breakthrough was the creation of a new drug class—biologics—differentiating manufactured drugs from living organisms. Thirty-five years later, biologics dominate new drug development and have given rise to the emergence of a subsequent drug class—biosimilars.

Biosimilars are biological medicines that contain a highly similar version of the active substance of an already approved biologic, commonly referred to as the reference product.[3] A biosimilar establishes high resemblance to the reference product in terms of quality characteristics, biological activity, safety, immunogenicity, and efficacy based on comprehensive comparability studies. Once similarity is established, regulatory agencies, such as the FDA, allow at least 1 of the approved indications for the reference biologic agent to be listed as an indication of the biosimilar.[4] The availability of biosimilars is an opportunity to lower health care expenditures due to inherent price competition with their reference product.[5] Specifically, the approval of oncologic biosimilars arrives at a time when the cost of cancer drugs exceeds that of any other therapeutic category.[4] Despite expected cost advantages of the biosimilars, established safety and efficacy profiles, a long history of their use for nononcology indications in Europe, and their successful application in nonmalignant conditions, the uptake and manufacturing of oncology biosimilars in the United States have been slow, partly due to existing patents for anticancer biologics.[6] Two supportive care oncology biosimilars are available in the United States; their reference product is filgrastim. In this review, we analyze hurdles facing biosimilar use

Table 1. Differences Between Biosimilars and Biologic Agents, Brand-Name Drugs, and Their Generic Equivalents[a]

Characteristic	Nonbiologic Generic	Biologic	Biosimilar
Size	Small	Large	
Molecular weight	<1000 Da	200-1000 times the size of a small molecule	4000 to >14 000 Da
Structure	Simple to relatively simple	Complex	Biosimilars potentially have structural variations but are designed to be highly similar to their biologic reference product
Manufacturing	Predictable and bioequivalent to the brand name	Piece of DNA added to a cell; a protein is generated and becomes the biologic	Stepwise process to make a similar compound
Complexity	Easy to characterize	Difficult to characterize	Difficult to characterize
Stability	Stable	Sensitive to handling and storage	Sensitive to handling and storage
Immunogenicity	Low potential	High potential	Goal is to demonstrate that immunogenicity of the biosimilar is not increased relative to the reference product; this process is assessed by evaluating the upper limit of immunogenicity incidence based on experience with the reference product
Approval requirements	Small clinical trials in healthy volunteers	Standard FDA guidelines	Large clinical trials; development of a biosimilar must include ≥1 clinical study, including assessment of immunogenicity and PK or PD; licensure pathway for a biosimilar is an abbreviated pathway
Class example	Loop diuretics, nonsteroidal anti-inflammatory agents	Therapeutic proteins and monoclonal antibodies	Therapeutic proteins and monoclonal antibodies

Abbreviations: US FDA, Food and Drug Administration; PD, pharmacodynamics; PK, pharmacokinetics.

[a] Data obtained from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. Accessed June 13, 2017.

Table 2. Biosimilars Approved and Under Consideration[a]

Biosimilar Status	Biosimilar Name[b]	Product (Brand Name)
FDA approved[c,d]	Adalimumab-atto (Amjevita)	Adalimumab (Humira)
	Etanercept-szzs (Erelzi)	Etanercept (Enbrel)
	Filgrastim-sndz (Zarxio)	Filgrastim (Neupogen)
	tbo-Filgrastim (Granix)	Filgrastim (Neupogen)
	Infliximab-abda (Renflexis)	Infliximab (Remicade)
	Infliximab-dyyb (Inflectra)	Infliximab (Remicade)
Phase 3 trials (completed or under way)[d]	BCD-021 (Biocad) ABP 215 (Amgen)	Bevacizumab (Avastin)
	ABP 494 (Amgen)	Cetuximab (Erbitux)
	GP2013 (Sandoz) BCD-020 (Biocad) CT-P10 (Celltrion) RTXM83 (mAbxience)	Rituximab (Rituxan)
	ABP 980 (Amgen) CT-P6 (Celltrion)	Trastuzumab (Herceptin)

Abbreviation: FDA, US Food and Drug Administration.

[a] Data obtained from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. Accessed June 13, 2017.

[b] Brand names appear in parentheses for FDA-approved drugs; manufacturer names appear in parentheses for drugs in phase 3 trials.

[c] FDA-approved biosimilars: all interchangeable except for tbo-filgrastim.

[d] Biosimilars in phase 3 trials (completed or under way): 351(k) Biosimilar Pathway application under first cycle review, goal date estimated in 2017.

in oncology in the United States and propose solutions to perceived barriers in their adoption.

Commonly Asked Questions

Are Biosimilars the Same as Generic Drugs?

Generic medications are small molecules that are chemically identical to the corresponding original agent; they are easily manufactured due to reproducible chemical processes (**Table 1** and **Table 2**).[7] Generics have the same active ingredients as brand-name medications and have demonstrated no significant difference in the rate and extent to which the active ingredient becomes available when administered under comparable conditions.[8] Generics are similar in terms of dosing, safety, strength, route of administration, quality, and intended use to

their brand-name counterparts.[9] Moreover, generics are bioequivalent to brand-name drugs.

Biologics are complex molecules synthesized in living organisms with inherent minor variations based on process; unlike a chemically synthesized drug, the process and product for biologics are both regulated. Biologics are not chemically identical batch to batch and neither are their biosimilars, despite being synthesized to be highly similar. In contrast to generics, biosimilars are allowed minor differences because they are created through processes found in living organisms that are less predictable and reproducible.[10] Differences between biosimilars and their reference drugs can lead to minor variations in molecular structure and immunogenicity. The application of the term *biosimilar* is meant to describe a high degree of similarity to the reference product rather than demonstrating clinical benefit.[11] These differences have led regulatory agencies to implement alternative rules and guidelines for the approval process of biosimilars than those for generics, just as agencies developed alternative guidelines for biologics when they were introduced more than 30 years ago.

To prove that a generic is equivalent to a brand-name drug, manufacturers have to establish bioequivalence in the laboratory.[12] A generic and brand-name drug are considered bioequivalent if they release their active ingredient into the bloodstream in the same amount and at the same rate, with an expected similar effect at the site of physiologic activity. Since the therapeutic chemical compound is the same molecule in the generic and brand-name drugs, the efficacy of the 2 is considered to be no different. Conversely, manufacturers must conduct clinical studies to demonstrate comparable efficacy of a biosimilar. These trials are performed after extensive structural and functional characterization of the biosimilar to justify proceeding with the clinical study in humans.[13]

What Are the Regulatory Requirements to Approve a Biosimilar in the United States?

The FDA regulates biosimilars and generics differently. The complexity of production, as well as the differences in molecular structure and immunogenicity, necessitated these alternative guidelines. Generics are approved under the Abbreviated New Drug Application 505(j).[14,15] The Biologic Price Competition and Innovation Act of 2009 (BPCI Act), enacted as part of the Affordable Care Act (ACA) of 2008, created an abbreviated licensure pathway for biosimilars to FDA-approved biological drugs (approved reference product; Section 351[k]), reflecting clear statutory and scientific distinction between generic and biosimilar drugs.[16,17] After testing the drug in a clinical trial, the manufacturer sends the FDA a New Drug Application. For drugs composed of biologic materials, instead of a New Drug Application, the manufacturer submits a Biologics License Application. Whether a New Drug Application or a Biologics License Application, the application includes the drug's clinical trial results, manufacturing information to demonstrate that the company can properly manufacture the drug, and the company's proposed label for the drug. The label provides necessary information about the drug, including uses for which it has been shown to be effective, possible risks, and how to use it.

If an FDA review shows that the benefits outweigh known risks and that the drug can be manufactured with assured quality, the drug is approved and can be marketed in the United States. Although the application process for a biosimilar drug is less complex than for its reference product, it is more complicated than the process undertaken for a generic drug. Under Section 351(k), a biosimilar application must contain data demonstrating biosimilarity. This information comprises analytical, animal, and clinical studies, including assessments of immunogenicity, pharmacodynamics, and pharmacokinetics, and a determination from the FDA regarding the necessity of the proposed biosimilar agent.[18] In addition, a biosimilar must meet criteria summarized in eTable 1 in the Supplement.[19]

Is Extrapolation to Additional Indications Appropriate?

Whereas a biologic's manufacturer conducts randomized clinical trials for each desired indication, extrapolation of safety and efficacy data from one biosimilar indication to another may be considered by the FDA provided that biosimilarity to the reference product has been convincingly demonstrated through a comprehensive comparative program. This biosimilarity must be established in a key indication suitable to detect clinically relevant differences between the biosimilar and reference product.[20] Extrapolation should take into account the shared mechanism of action in the requested indication and perceived risks that could emerge from treating different patient populations. If the relevant mechanism of action of the active substance is the same in the tested and expanded indications, extrapolation is less problematic.[20] When the mechanism of action is more complex and potentially different from one indication to another, additional pharmacologic data may be necessary to provide reassurance that the biosimilar and reference product will behave similarly across indications. Both the FDA and the European Medicines Agency (EMA) approve a biosimilar agent based on the totality of preclinical and clinical evidence. Although 1 approved indication does not guarantee that other indications will follow or that either the FDA or the EMA will approve a biosimilar that was approved by its counterpart, extrapolation often occurs.[21] The FDA requires that 5 criteria be met for scientific justification of extrapolation,[22] and the EMA uses 3 scientific criteria to approve indication extrapolation[23] (summarized in eTable 1 in the Supplement).

Extrapolation requirements for both regulatory agencies in the United States and Europe may reassure clinicians who have suggested that independent confirmatory trials are needed for every indication and in every disease stage. In a survey conducted among 1201 specialty physicians, including oncologists, Cohen et al[24] reported that only 12% of physicians are comfortable with the concept of extrapolation, highlighting the need for better understanding of barriers to this concept and the educational gap among clinicians regarding extrapolation. Regulatory authorities agree that a confirmatory trial is needed only in the most sensitive or representative patient population. Once the confirmatory trial is completed, clinically meaningful differences in subsequent trials for additional indications are unlikely to be detected. Moreover, in the setting of limited resources and financial constraints, extrapolation represents a cost-saving measure.

Can the Use of Biosimilars and Generics Save Money?

Almost 80% of prescriptions in the United States are filled using generic products, with estimated savings of approximately $158 billion in 2010.[25] The use of generics can decrease the cost of care in many instances, at least when generic versions of brand-name drugs can be manufactured and prescribed. In 2005, biologics ac-

counted for 32% of the $9.5 billion Medicare Part B drug spending and, by 2014, they represented 62% of the $18.5 billion total.[26] This amount underscores the effect of biologics on health care drug cost. As the market share for biologics increases, the opportunity for savings will likely grow. As a result of their molecular complexity, synthesis process, and clinical trial requirements, the cost differential between a reference biologic and its biosimilar is likely to be significantly more narrow than between a brand-name and generic drug. Therefore, biosimilars are not expected to produce cost savings with the same magnitude as generics.[13] Although biosimilars are often developed by competing manufacturers, one could envision that manufacturers who are facing patent expirations of their biologic products might consider the pursuit of biosimilar development. Theoretically, the perceived financial loss of drugs with expired patents might be offset by the incremental use of their corresponding biosimilars.[13]

It is yet to be determined whether the availability of biosimilars will drive price competition, leading to lower health care costs—a desired outcome in oncology given how the cost of cancer care exceeds all other health care expenditures.[27] Biosimilars are expected to be priced approximately 20% to 30% lower than their reference biologic, which may translate into substantial cost savings to the health care system.[28] However, the experience with growth factor biosimilars demonstrated that wholesale prices were listed at 15% less than filgrastim as opposed to 30%, highlighting the uncertainty of actual discounts.[29] These lower prices do not suggest inferior efficacy and outcomes as some clinicians have feared[24,30,31]; to the contrary, the rigor mandated by the FDA to ensure safety and efficacy standards of biosimilars is consistent with requirements needed for reference products. Cost savings might be tempered by the administrative overheads resulting from pharmacovigilance programs intended to detect immunogenicity and adverse effects that could emerge when biosimilars are used commercially on the basis of extrapolation.[32] In a comprehensive analysis, Mulcahy et al[33] projected that the use of biosimilars will lead to a $44.2 billion reduction (range, $13 billion-$66 billion) in direct spending on biologics from 2014 to 2024, which represents 4% of the total biologic spending over the same period. This conclusion was based on a peer-reviewed literature search that encompassed 18 retrospective studies examining existing markets for biosimilars in European countries, 37 prospective analyses that projected prices and impact for biosimilars on US and European markets, 6 case series examining European experiences with individual biosimilars, and 23 non–peer-reviewed relevant articles, 6 of which were industry perspective. Collectively, the above information suggests that cost savings are expected with the use of biosimilars. However, as the US market is still nascent in adopting biosimilars, more prospective evaluations with continued monitoring of the cost structure and projected savings in the United States are needed. Payers' structure and planned reimbursement are different between the United States and Europe, being partially dependent on geographic location in the United States. In fact, infliximab remains on the formulary for most major payers despite the presence of its biosimilar that is offered at a 15% wholesale discount.[34] In addition, because no automated substitution between a biologic and a biosimilar (contrary to generics) is currently allowed, coupled with more emerging new biologics that have a long patent life, wider utilization of biosimilars in US markets remains speculative, affecting accurate cost reduction calculations. Cost implications can also be affected by rebate agreements between manufacturers and payers, in which incentives might be provided for allowing an expensive biologic vs a biosimilar.[34]

How Are Biosimilars Paid For?

Based on their large molecular size, most biologics are injected or infused. Self-administered, outpatient injected drug costs are dependent on specialty pharmacies and are paid for based on pharmacy benefit design, where insurers pay for a portion of the cost and patients are responsible for the remaining balance, reflecting their medical benefit design for coinsurance and copay. When dispensed in a physician office setting, fee-for-service payments for biologics are based on the average sale price (ASP) plus 4.3% to theoretically cover acquisition and inventory cost.[35] Although payments for biologics dispensed in the inpatient setting can be part of a bundled payment program, the outpatient setting may be eligible for discount programs, such as 340B.[36,37] Understanding billing and reimbursement implications within different settings is critical to project the financial implications of biosimilars.

Centers for Medicaid & Medicare guidelines for biosimilar reimbursement have not been easily understood and could represent another barrier to wider adoption. Before an ASP is established for a biosimilar, Medicare is likely to issue payments factoring wholesale acquisition cost plus a surcharge (likely 4%-6% of the wholesale acquisition cost) of the biosimilar.[31,32] Once an ASP for the biosimilar is established, Medicare payments are expected to include the ASP of the biosimilar plus 4% to 6% of the reference product as a surcharge.[38] For example, consider a biologic with an ASP of $1000. Using the ASP + 6% formula, reimbursement will be at $1060, which will result in a margin of $60 and a margin rate of 6%. If the ASP of this biologic's biosimilar is $800, reimbursement will be at $860 ($800 + [$1000 × 6%] = $860). This translates into a margin of $60 and margin rate of 7.5%. Theoretically, using the same add-on rate of 6% of the reference product, financial incentives for physicians are the same and, essentially, practices are not financially penalized for prescribing the lower-priced biosimilar product. In both cases, the practice is reimbursed for the cost of acquisition of the respective reference or biosimilar plus the same margin dollar amount. Lastly, from the physician fee payment perspective, one J-Code, a unique drug code used for billing purposes, is likely to be issued for all biosimilars of a given reference product as opposed to individual codes.[39,40]

Would Policy Changes in the United States Affect Biosimilars?

The ACA has brought on many changes and challenges to all stakeholders in health care, some of which might change further as the political landscape in the United States is altered and efforts to repeal and/or replace various components of the ACA continue. Thought leaders and policymakers have argued that repealing the ACA in its entirety may be impractical and that certain statutory clauses will likely continue. It is our opinion that the BPCI Act is likely to remain in effect and unlikely to be replaced in the near term.[19,41] Regardless of the ACA's fate, the Medicare Access and CHIP Reauthorization Act (MACRA) is destined to remain since this law was passed in 2015 with bipartisan support in both houses of the US Congress. MACRA emphasizes quality within the provision of health care rather than quantity, focuses on proper resource utilization, and supports practice improvements and care coordination in addition to

Table 3. Filgrastim Compared With FDA-Approved Biosimilars: Approval Pathway, Pharmacokinetics, and Indication

Characteristic	Reference Product	First Biosimilar Drug	Second Biosimilar Drug
Generic name	Filgrastim[44]	tbo-Filgrastim[45]	Filgrastim-sndz[46]
Trade name	Neupogen	Granix	Zarxio
Manufacturer	Amgen	Teva	Sandoz
Initial FDA approval date	1991	2012	2016
FDA approval pathway	Innovator biologic through 351(a) pathway[a]	Approved through 351(a) pathway	Approved as a biosimilar through 351(k) pathway
Interchangeable with filgrastim	NA	No; not approved via US biosimilar 351(k) pathway	Yes
FDA-approved indications and dose			
Febrile neutropenia in nonmyeloid cancers undergoing myeloablative chemotherapy followed by transplant	10 μg/kg	Not FDA indicated	10 μg/kg
Febrile neutropenia in nonmyeloid cancers following myelosuppressive chemotherapy	5 μg/kg	5 μg/kg	5 μg/kg
Febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy	5 μg/kg	Not FDA indicated	5 μg/kg
Harvesting of peripheral blood stem cells	10 μg/kg	Not FDA indicated	10 μg/kg
Neutropenic disorder, chronic, symptomatic	5-6 μg/kg	Not FDA indicated	5-6 μg/kg
Radiation injury of bone marrow, acute exposure of myelosuppressive radiation doses	10 μg/kg	Not FDA indicated	Not FDA indicated

Abbreviations; FDA, US Food and Drug Administration; NA, not applicable.

[a] Innovator biologics are licensed under Section 351(a) of the Public Health Service Act, whereas biosimilars are licensed under 351(k), which is an abbreviated developmental pathway. The 351(k) pathway allows drug licensure based on preclinical and clinical data already established from the innovator product. The 351(k) pathway was established in 2010 in response to biosimilar applications under the Biologics Price Competition and Innovation Act. The 351(a) development pathway entitles a manufacturer to 12 years of marketing exclusivity vs the 12 months for a 351(k) biosimilar.

other components.[42,43] MACRA, coupled with value-based care, may shape future practice patterns, including those involving biosimilars. Health care professionals will be expected to prescribe higher-value and lower-cost therapies if available, while manufacturers will attempt to demonstrate actual value derived from their products to help ensure regulatory approval and market uptake. In this challenging market, biosimilars are poised to succeed given the relatively favorable value vs cost ratio, provided regulatory requirements are fulfilled. A detailed discussion on the effect of policy on biosimilars is beyond the scope of this review.

Discussion

There is little doubt that biosimilars will be incorporated into treatment regimens for various malignant diseases in the United States in the coming years, but the rate and depth of adoption, as well as the savings impact, are difficult to forecast. Practicing oncologists rely on clinical guidelines published by the American Society of Hematology, the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) to prescribe therapies and ensure proper reimbursement for dispensed drugs. The incorporation of biosimilars in clinical pathways as supported by the ASCO and NCCN may lead to wider adoption of these agents. Because biosimilars will likely cost less than their reference products, they may be a preferred option in a clinical pathway, replacing a competitor drug of similar efficacy in a specific disease state.

Both the ASCO and NCCN Colony Stimulating Growth Factor Guidelines endorse the use of their biosimilars (**Table 3**).[19,47] Experience with biosimilars in Europe may provide reassurance to US-based payers and prescribers that biosimilars are safe and effective since this approach has been successfully implemented. Proper market utilization could generate healthy competition and price reduction, with both leading to better patient access. The public's and health care professionals' acceptance of biosimilars will require education despite mandates from insurance carriers for their preferential use. Educating health care professionals and patients on the rigor of the regulatory requirements needed to render a biosimilar with FDA approval and its distinction from a generic product is critical to the success of its platform.[48,49] With recognition of price differences, additional use of biosimilars is anticipated and market acceptance might improve. Cost-saving opportunities with biosimilars will require assessment of the administrative expenses needed for regulatory and postapproval pharmacovigilance programs associated with these agents.

Despite the prospect for a financial advantage with biosimilar use, there remains unanswered questions. As newer treatment entities infiltrate the oncology market, are we to anticipate development of biosimilars for all various therapeutic antibodies, and should we use traditional end points in confirmatory studies of biosimilars?[50] It remains unclear whether switching between a reference product and its biosimilar will compromise long-term efficacy, especially with extrapolation. If different end points are needed for various patient populations, how might this need affect extrapolation, and would such an approach remain scientifically sound? As suggested by some, other clinical end points, such as response rates and changes in tumor measurements that focus on differences in efficacy vs demonstrating efficacy, may be better.[20] Although safety is usually preliminarily addressed during the approval process, real-world evidence may reveal toxicity profiles different from those observed in clinical studies. Institution of postapproval registries for biosimilars might shed some light on practice patterns and observed toxic effects, both of which might shape further monitoring and approval of additional biosimilars. Concerns about safety after commercialization have been raised with the use of biosimilars in rheumatology.[51] In addition, antibodies induced by epoetin

alfa (Eprex) contributed to pure red cell aplasia in Europe, highlighting the importance for continued vigilance of safety and immunogenicity.[52,53]

Among the myriad factors affecting the rate and depth of biosimilar adoption in oncology, none may be as significant as the clinical setting in which biosimilars are used. We identify 4 such clinical scenarios in which stakeholders in oncology may have varying thresholds for biosimilar adoption: supportive care, long-term treatment of non–life-threatening disease, palliative treatment of life-threatening disease, and curative treatment of life-threatening disease. The willingness of patients and physicians to accept extrapolation evidence for treatment selection for curative, life-threatening disease settings may be very different from that for supportive care. To date, the 2 approved biosimilars in the United States are myeloid growth factors used in supportive care (Table 3). The effect that these biosimilar growth factors have had on cost cannot be analyzed since both have been available for a short time. Also, given the changing reimbursement models, negotiating prices for biosimilars might lag behind due to uncertainty. Longer follow-up is needed to better understand market uptake for growth factor biosimilars. Furthermore, biosimilars that are used for active treatment of disease as opposed to supportive care might enter the market with more biologics patents expiring (eTable 2 in the Supplement). Whether the uptake of biosimilars used in active treatment differs from the uptake of those used in supportive care remains to be determined. Bevacizumab (global sales, $5.6 billion), transtuzumab (global sales, $5.1 billion), and infliximab (global sales, $7.5 billion) are all projected to have patent expiration within the next 5 years; all 3 drugs have biosimilars.[54]

Conclusions

There is broad evidence that biosimilars in general represent an opportunity to increase competition and lower health care cost without compromise to clinical outcomes. Educating clinicians and patients about the potential financial benefits of using biosimilars, their safety and equivalency, and their effect on health care expenditure is an important strategic approach if wider use of biosimilars is desired. Incorporation into respected clinical guidelines may be critical to their rate and depth of adoption, but payer programs and value-based care models may be the ultimate drivers of adoption because both physicians and patients assume greater financial risk for health care administered and received.

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REFERENCES

1. Janssen WF. The stories of the laws behind the labels. The US Food and Drug Administration. https://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm. Accessed May 5, 2017.
2. Zaykov AN, Mayer JP, DiMarchi RD. Pursuit of a perfect insulin. *Nat Rev Drug Discov*. 2016;15(6):425-439.
3. Belsey MJ, Harris LM, Das RR, Chertkow J. Biosimilars: initial excitement gives way to reality. *Nat Rev Drug Discov*. 2006;5(7):535-536.
4. Finkelstein JB. In US, biosimilars still await FDA decision. *J Natl Cancer Inst*. 2006;98(7):435.
5. Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. *N Engl J Med*. 2011;365(5):385-388.
6. Udpa N, Million RP. Monoclonal antibody biosimilars. *Nat Rev Drug Discov*. 2016;15(1):13-14.
7. Warren JB. Generics, chemisimilars and biosimilars: is clinical testing fit for purpose? *Br J Clin Pharmacol*. 2013;75(1):7-14.
8. Davit B, Braddy AC, Conner DP, Yu LX. International guidelines for bioequivalence of systemically available orally administered generic drug products: a survey of similarities and differences. *AAPS J*. 2013;15(4):974-990.
9. Zangeneh F, Dolinar R. Biosimilar drugs are not generics. *Endocr Pract*. 2016;22(1):6-7.
10. Mellstedt H. Anti-neoplastic biosimilars—the same rules as for cytotoxic generics cannot be applied. *Ann Oncol*. 2013;24(suppl 5):v23-v28.
11. Weise M, Bielsky MC, De Smet K, et al. Biosimilars: what clinicians should know. *Blood*. 2012;120(26):5111-5117.
12. Bate R, Mathur A, Lever HM, et al. Generics substitution, bioequivalence standards, and international oversight: complex issues facing the FDA. *Trends Pharmacol Sci*. 2016;37(3):184-191.
13. Camacho LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for US oncologists in clinical practice. *Cancer Med*. 2014;3(4):889-899.
14. Lemery SJ, Esteva FJ, Weise M. Biosimilars: here and now. *Am Soc Clin Oncol Educ Book*. 2016;35:e151-e157.
15. Lemery SJ, Ricci MS, Keegan P, McKee AE, Pazdur R. FDA's approach to regulating biosimilars. *Clin Cancer Res*. 2017;23(8):1882-1885.
16. Daller J. Biosimilars: a consideration of the regulations in the United States and European Union. *Regul Toxicol Pharmacol*. 2016;76:199-208.
17. Olech E. Biosimilars: rationale and current regulatory landscape. *Semin Arthritis Rheum*. 2016;45(5)(suppl):S1-S10.
18. US Department of Health and Human Services. Clinical pharmacology data to support a demonstration of biosimilarity to a reference product: guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf. Published December 2016. Accessed May 5, 2017.
19. Zelenetz AD, Ahmed I, Braud EL, et al. NCCN Biosimilars White Paper: regulatory, scientific, and patient safety perspectives. *J Natl Compr Canc Netw*. 2011;9(suppl 4):S1-S22.
20. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. *Blood*. 2014;124(22):3191-3196.
21. Burstein HJ, Schrag D. Biosimilar therapy for *ERBB2* (*HER2*)-positive breast cancer: close enough? *JAMA*. 2017;317(1):30-32.
22. Curigliano G, O'Connor DP, Rosenberg JA, Jacobs I. Biosimilars: extrapolation for oncology. *Crit Rev Oncol Hematol*. 2016;104:131-137.
23. Tsiftsoglou AS, Trouvin JH, Calvo G, Ruiz S. Demonstration of biosimilarity, extrapolation of indications and other challenges related to biosimilars in Europe. *BioDrugs*. 2014;28(6):479-486.
24. Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Adv Ther*. 2017;33(12):2160-2172.
25. Johansen ME, Richardson C. Estimation of potential savings through therapeutic substitution. *JAMA Intern Med*. 2016;176(6):769-775.
26. Sheingold S, Nguyen NX. Impacts of generic competition and benefit management practices on spending for prescription drugs: evidence from Medicare's Part D benefit. *Medicare Medicaid Res Rev*. 2014;4(1):mmrr.004.01.a01.
27. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-128.

28. Hede K. First biosimilar drug approved for sale in the United States. *J Natl Cancer Inst*. 2015;107(7):djv191.

29. Johnson SR. What happened to the innovation and competition Zarxio was supposed to spark? *Mod Healthc*. 2016;46(13):11.

30. Colgan S, Faasse K, Martin LR, Stephens MH, Grey A, Petrie KJ. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. *BMJ Open*. 2015;5(12):e008915.

31. Jacobs I, Singh E, Sewell KL, Al-Sabbagh A, Shane LG. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient Prefer Adherence*. 2016;10:937-948.

32. Roger SD, Goldsmith D. Biosimilars: it's not as simple as cost alone. *J Clin Pharm Ther*. 2008;33(5):459-464.

33. Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf. Published 2014. Accessed February 16, 2017.

34. Hakim A, Ross JS. Obstacles to the adoption of biosimilars for chronic diseases. *JAMA*. 2017;317(21):2163-2164.

35. Ward MM. Medicare reimbursement and the use of biologic agents: incentives, access, the public good, and optimal care. *Arthritis Care Res (Hoboken)*. 2010;62(3):293-295.

36. Kantarjian H, Chapman R. Value of the 340B Drug Discount Program. *JAMA Oncol*. 2015;1(8):1029-1030.

37. Kantarjian HM, Chapman R. Role of the 340B Drug Discount Program in recent cancer care trends. *J Oncol Pract*. 2015;11(4):303-307.

38. CMS.gov. Centers for Medicare & Medicaid Services. Part B biosimilar biological product payment and required modifiers. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html. Updated November 22, 2016. Accessed May 5, 2017.

39. Falit BP, Singh SC, Brennan TA. Biosimilar competition in the United States: statutory incentives, payers, and pharmacy benefit managers. *Health Aff (Millwood)*. 2015;34(2):294-301.

40. Malik AN, Keeping K, Fletcher-Louis M. US payer expectations for reimbursement of biosimilars. *Value Health*. 2015;18(7):A545.

41. Paradise J. The legal and regulatory status of biosimilars: how product naming and state substitution laws may impact the United States healthcare system. *Am J Law Med*. 2015;41(1):49-84.

42. Mullins A. Making sense of MACRA, part 2: value-based payment and your future. *Fam Pract Manag*. 2017;24(1):12-15.

43. Tempero M. Mad about MACRA. *J Natl Compr Canc Netw*. 2017;15(2):137.

44. Neupogen [package insert]. Thousand Oaks, CA; Amgen Inc, 2015.

45. Granix [package insert]. North Wales, PA: Teva Pharmaceuticals USA Inc; 2017.

46. Zarxio [package insert]. Princeton, NJ: Sandoz Inc; 2015.

47. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015;33(28):3199-3212.

48. Ebbers HC, Crow SA, Vulto AG, Schellekens H. Interchangeability, immunogenicity and biosimilars. *Nat Biotechnol*. 2012;30(12):1186-1190.

49. Ebbers HC, Pieters T, Leufkens HG, Schellekens H. Effective pharmaceutical regulation needs alignment with doctors. *Drug Discov Today*. 2012;17(3-4):100-103.

50. Gonçalves J, Araújo F, Cutolo M, Fonseca JE. Biosimilar monoclonal antibodies: preclinical and clinical development aspects. *Clin Exp Rheumatol*. 2016;34(4):698-705.

51. Braun J, Kudrin A. Switching to biosimilar infliximab (CT-P13): evidence of clinical safety, effectiveness and impact on public health. *Biologicals*. 2016;44(4):257-266.

52. Schellekens H. The first biosimilar epoetin: but how similar is it? *Clin J Am Soc Nephrol*. 2008;3(1):174-178.

53. Mikhail A, Farouk M. Epoetin biosimilars in Europe: five years on. *Adv Ther*. 2013;30(1):28-40.

54. Reinke T. Biosimilars ready, at last, to make their entrance: stars are born or do they fizzle? *Manag Care*. 2017;26(3):20-23.