Biosimilars in Oncology in the United States
A Review

Chadi Nabhan, MD, MBA; Sandeep Parsad, PharmD; Anthony R. Mato, MD, MSCE; Bruce A. Feinberg, DO

**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 biosimilars 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.

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—differiating 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...
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). 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. Generics are similar in terms of dosing, safety, strength, route of administration, quality, and intended use to

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonbiologic Generic</th>
<th>Biologic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small</td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt;1000 Da</td>
<td>200-1000 times the size of a small molecule</td>
<td>4000 to &gt;14 000 Da</td>
</tr>
<tr>
<td>Structure</td>
<td>Simple to relatively simple</td>
<td>Complex</td>
<td>Biosimilars potentially have structural variations but are designed to be highly similar to their biologic reference product</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Predictable and bioequivalent to the brand name</td>
<td>Piece of DNA added to a cell; a protein is generated and becomes the biologic</td>
<td>Stepwise process to make a similar compound</td>
</tr>
<tr>
<td>Complexity</td>
<td>Easy to characterize</td>
<td>Difficult to characterize</td>
<td>Difficult to characterize</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable</td>
<td>Sensitive to handling and storage</td>
<td>Sensitive to handling and storage</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Low potential</td>
<td>High potential</td>
<td>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</td>
</tr>
<tr>
<td>Approval requirements</td>
<td>Small clinical trials in healthy volunteers</td>
<td>Standard FDA guidelines</td>
<td>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</td>
</tr>
<tr>
<td>Class example</td>
<td>Loop diuretics, nonsteroidal anti-inflammatory agents</td>
<td>Therapeutic proteins and monoclonal antibodies</td>
<td>Therapeutic proteins and monoclonal antibodies</td>
</tr>
</tbody>
</table>

**Table 2. Biosimilars Approved and Under Consideration**

<table>
<thead>
<tr>
<th>Biosimilar Status</th>
<th>Biosimilar Name*</th>
<th>Product (Brand Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approved*</td>
<td>Adalimumab-atto</td>
<td>Adalimumab (Humira)</td>
</tr>
<tr>
<td></td>
<td>(Amjevita)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Etanercept-szzs</td>
<td>Etanercept (Enbrel)</td>
</tr>
<tr>
<td></td>
<td>(Erezzi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filgrastim-snld</td>
<td>Filgrastim (Neupogen)</td>
</tr>
<tr>
<td></td>
<td>(Zarzio)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tbo-Filgrastim</td>
<td>Filgrastim (Neupogen)</td>
</tr>
<tr>
<td></td>
<td>(Granix)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab-abda</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td></td>
<td>(Renflexis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab-dyyb</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td></td>
<td>(Inflectra)</td>
<td></td>
</tr>
<tr>
<td>Phase 3 trials (completed or under way)*</td>
<td>BCD-021 (Biocad)</td>
<td>Bevacizumab (Avastin)</td>
</tr>
<tr>
<td></td>
<td>ABP 215 (Amgen)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABP 494 (Amgen)*</td>
<td>Cetuximab (Erbilux)</td>
</tr>
<tr>
<td></td>
<td>GP2013 (Sandoz)</td>
<td>Rituximab (Rituxan)</td>
</tr>
<tr>
<td></td>
<td>BCD-020 (Biocad)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT-P10 (Celltrion)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CTM83 (mAbxience)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABP 980 (Amgen)</td>
<td>Trastuzumab (Herceptin)</td>
</tr>
<tr>
<td></td>
<td>CT-P6 (Celltrion)</td>
<td></td>
</tr>
</tbody>
</table>

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


*FDA-approved biosimilars; none are interchangeable; tbo-filgrastim was not approved under 351(k) Biosimilar Pathway.

*Biosimilars in phase 3 trials (completed or under way).

*351(k) Biosimilar Pathway application under first cycle review, goal date estimated in 2017.

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

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their brand-name counterparts. Moreover, generics are bio-
equivalent to brand-name drugs.

Biologics are complex molecules synthesized in living organ-
isms with inherent minor variations based on process; unlike a chemi-
cally 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 differ-
ences because they are created through processes found in living
organisms that are less predictable and reproducible. Differences
between biosimilars and their reference drugs can lead to mi-
nor 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 clini-
cal benefit. These differences have led regulatory agencies to imple-
ment alternative rules and guidelines for the approval process of bio-
similars 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. 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 com-
pound is the same molecule in the generic and brand-name drugs,
efficacy of the 2 is considered to be no different. Conversely,
manufacturers must conduct clinical studies to demonstrate com-
parable efficacy of a biosimilar. These trials are performed after ex-
tensive structural and functional characterization of the biosimilar
to justify proceeding with the clinical study in humans.

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

The FDA regulates biosimilars and generics differently. The com-
plexity of production, as well as the differences in molecular struc-
ture and immunogenicity, necessitated these alternative guide-
lines. Generics are approved under the Abbreviated New Drug
Application 505(j). The Biologic Price Competition and Innova-
tion 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 dis-
tinction between generic and biosimilar drugs. 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 Li-
cense 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 com-
pany can properly manufacture the drug, and the company’s pro-
posed label for the drug. The label provides necessary information
about the drug, including uses for which it has been shown to be ef-
efective, 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 under-
taken for a generic drug. Under Section 351(k), a biosimilar applica-
tion must contain data demonstrating biosimilarity. This informa-
tion comprises analytical, animal, and clinical studies, including
assessments of immunogenicity, pharmacodynamics, and pharma-
kinetics, and a determination from the FDA regarding the neces-
sity of the proposed biosimilar agent. In addition, a biosimilar must
meet criteria summarized in eTable 1 in the Supplement.

Is Extrapolation to Additional Indications Appropriate?

Whereas a biologic’s manufacturer conducts randomized clinical
trials for each desired indication, extrapolation of safety and effi-
cacy data from one biosimilar indication to another may be consid-
ered by the FDA provided that biosimilarity to the reference prod-
uct 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. 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. 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 refer-
ence 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 indi-
cations will follow or that either the FDA or the EMA will approve a
biosimilar that was approved by its counterpart, extrapolation
often occurs. The FDA requires that 5 criteria be met for scientific
justification of extrapolation, and the EMA uses 3 scientific crite-
rion to approve indication extrapolation (summarized in eTable 1 in
the Supplement).

Extrapolation requirements for both regulatory agencies in the
United States and Europe may reassure clinicians who have sug-
gested 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. re-
ported that only 12% of physicians are comfortable with the con-
cept of extrapolation, highlighting the need for better understand-
ing 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 repre-
sentative patient population. Once the confirmatory trial is com-
pleted, clinically meaningful differences in subsequent trials for ad-
ditional 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?

Almmost 80% of prescriptions in the United States are filled using ge-
eric products, with estimated savings of approximately $158 bil-

lion in 2010. 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 feared24,30,31; 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 pharmaceutical 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 al33 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.39,41 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
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).39,47 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 healthcare 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, with both leading to better patient access. The public’s and healthcare 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

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

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

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

<sup>a</sup>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.
alfa (Eprex) contributed to pure red cell aplasia in Europe, highlighting the importance for continued vigilance of safety and immunogenicity.

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.

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.

ARTICLE INFORMATION

Accepted for Publication: May 17, 2017.
Published Online: July 20, 2017.
Correction: This article was corrected on August 24, 2017, to fix errors in Table 2 and Table 3.

Author Contributions: Drs Nabhan and Feinberg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis, or interpretation of data: Nabhan.

Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: Nabhan. Administrative, technical, or material support: Nabhan, Parsad, Mato. Supervision: Nabhan, Feinberg.

Conflict of Interest Disclosures: Drs Nabhan and Feinberg are employed by Cardinal Health Inc. They both hold leadership positions and own stocks in Cardinal Health Inc. No other conflicts were reported.

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