

Conclusion

As cytotoxic chemotherapy-induced FN may lead to serious complications of infection and mortality, initiating antimicrobial therapy is recommended for this patient population. Before initiating antibiotic therapy, it is crucial to perform a risk assessment to determine whether the therapy should be oral or intravenous, inpatient or outpatient, and patient needs for the duration of therapy. Risk assessment also plays a key role in determining whether G-CSF should be initiated for primary prophylaxis. Guidelines suggest that G-CSF may be needed to boost the immune system of high-risk patients, but G-CSF should initially be avoided in low-risk patients. In cases of intermediate risk, additional patient risk factors need to be weighed.

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Pricing and Contracting in Granulocyte Colony-Stimulating Factors and Biosimilars for Febrile Neutropenia

Introduction

Annual spending on biologic medications has been on the rise. It is estimated that biologic drugs, defined as complex, protein-based, large-molecule compounds designed to treat complicated disease states, accounted for \$200 billion to \$210 billion of global spending on medicines in 2016.^{1,2} With such rises in healthcare spending, it is important to consider the economic implications and potential of adopting effective cost-saving measures wherever possible. Biosimilars can offer an opportunity in terms of cost-saving potential, with an estimated potential of \$44.2 billion in savings in biologic drug spending in the United States from 2014 to 2024.³

The cost savings could ultimately provide huge benefits to patients, healthcare providers, and all payers involved in the healthcare system, which is especially important in an era of rapidly rising healthcare costs.³

A biosimilar is a biological product that is approved for use based on chemical, molecular, and structural similarities to an already approved biological drug, known as the reference drug or originator product.² According to the FDA, a biosimilar must show no clinically significant differences in its efficacy and safety profile in comparison with its reference product.⁴ The introduction of biosimilars into the pharmaceutical market has lowered medication costs while also allowing expanded »

TABLE 1. List of Approved Biosimilars in the United States as of August 2017²³⁻²⁸

PRODUCT NAME	PROPRIETARY NAME	REFERENCE/ORIGINATOR BIOLOGIC	APPROVAL DATE
Adalimumab-atto	Amjevita	Humira (adalimumab)	September 2016
Etanercept-szszs	Erelzi	Enbrel (etanercept)	August 2016
Filgrastim-sndz	Zarxio	Neupogen (filgrastim)	March 2015
Infliximab-abda	Zarxio	Remicade (infliximab)	April 2017
Infliximab-dyyb	Inflectra	Remicade (infliximab)	April 2016

patient access to new treatments.⁵ One example in which the economic and facilitative impact of biosimilars can be seen is the granulocyte colony-stimulating factor (G-CSF) market; there were notable changes in the cost and accessibility of the medication class after the introduction of biosimilars.

Landscape of the G-CSF Market Before the Introduction of Biosimilars

Filgrastim, a G-CSF used to decrease the incidence of febrile neutropenia in patients with malignancies who are receiving myelosuppressive therapy, was first marketed in the North American and European markets by Amgen Inc in the early 1990s under the brand name Neupogen.^{6,7} Neupogen was able to dominate the international G-CSF market, achieving \$1.3 billion in sales in 1999 due to the lack of a competitor product in the North American market.^{7,8} To further capitalize on the G-CSF market, Amgen Inc released a pegylated, long-acting formulation of filgrastim under the brand name Neulasta (pegfilgrastim), which was approved by the FDA in 2002.⁹ Neulasta sales increased to 51% of the international G-CSF market in 2007, earning \$5.6 billion, followed by Neupogen, which was worth 24% of the market share, or \$1.3 billion in sales.⁷

In 2012, Teva launched a recombinant version of filgrastim, tbo-filgrastim, under the brand name Granix in the United States market; its average wholesale price was discounted 15%, in comparison with Neupogen.¹⁰ Teva's product gained a 34% share of the short-acting G-CSF hospital market within just 17 months of its launch, which grew to an approximate 40% share after 34 months.^{11,12} Despite the increase in competition in the overall North American G-CSF market with the introduction of Granix, Neulasta currently does not face any competition in the long-acting G-CSF market, because there are no approved pegfilgrastim biosimilars available at the time of publication of this article (see **Table 1**¹³⁻¹⁸ for a list of approved biosimilars in the United States).¹⁸

Biosimilar Development, Regulations, and Approval Pathway in the United States

In 2010 the Patient Protection and Affordable Care Act was signed into law; it amended the Public Health Service Act (PHSA) to include the Biologics Price Competition and Innovation Act. This amendment created an abbreviated regulatory pathway for biosimilar approval through the FDA.¹⁹ The new pathway allowed biosimilars an expedited licensure process under the 351(k) section of the PHSA if the biosimilar product was shown to be highly similar in clinical efficacy, purity, potency, and safety to a previously FDA-approved reference or originator biologic.^{4,19} The reference biologic product is required to have been approved through the 351(a) Biologics License Application pathway, which entitles manufacturers to a period of 12 years of exclusivity during which biosimilars cannot be approved.²⁰ In comparison with the 351(a) pathway, the 351(k) pathway for biosimilars is less defined in terms of regulation, because the FDA evaluates each product on a case-by-case basis and it may not require certain clinical studies and evidence trials to be conducted.^{4,20} Filgrastim-sndz (Zarxio), a G-CSF biosimilar of Neupogen, was approved in 2015, the first biosimilar to be approved in the United States through the 351(k) pathway.^{21,22}

Although the FDA grants flexibility in the regulatory requirements for the 351(k) pathway, it has issued draft guidance documents to clarify the approach it takes when evaluating biosimilar products for approval.²³ To establish a foundation of comparability, the FDA requires analytical data demonstrating structural, functional, and biochemical similarity of a biosimilar candidate to a reference product.⁴ Tests such as nuclear magnetic resonance imaging, high-performance liquid chromatography, and enzyme-linked immunosorbent assays can be used to distinguish differences and similarities between 2 products.²⁴ According to the FDA, minor structural variations such as differences in inactive ingredients or posttranslational modifications that

TABLE 2. FDA Requirements for Biosimilar Approval^{4,25,26}

Analytical data demonstrating structural, functional, and biochemical similarity to an approved biologic reference product
At least 1 human pharmacodynamic or pharmacokinetic study against an approved biologic reference product
Detailed analysis of originator product to determine shelf life and boundaries of acceptable features for the candidate biosimilar
Clinical efficacy trials, safety profile data, animal study data, stability and formulation studies, and additional pharmacodynamic and pharmacokinetic studies if required
Immunogenicity studies demonstrating risk of immune system-mediated life-threatening events
Data extrapolation and scientific justification if the sponsor company is seeking additional approved indications for candidate biosimilar

do not affect clinical utility are not preclusions to approval.²⁵ In addition to analytical and structural data and tests, the FDA can request preclinical and clinical data if deemed appropriate. Although the FDA requires a minimum of 1 human pharmacodynamic or pharmacokinetic (PK) study, additional clinical efficacy trials, PK studies, and safety profile data for biosimilar candidates may be requested for further evaluation to confirm safety and efficacy.^{4,25} Critical safety studies, such as immunogenicity testing, are required unless otherwise stated by the FDA, to minimize the risk of life-threatening adverse events.²⁰

Overall, the FDA takes a “totality of evidence approach” in its evaluation process, in which it extensively considers all analytical and structural data comparisons in addition to animal, pre-clinical, clinical, and safety studies to ensure that no clinically significant differences exist between the biosimilar candidate and the reference product (see **Table 2**^{4,25,26} for additional information).⁴

The Impact of G-CSF Biosimilars on the G-CSF Market

The first G-CSF biosimilar was approved in 2008 in the European Union (EU). Since then, 6 other G-CSF biosimilars have been approved in the EU, leading to price reductions in both the biosimilar/reference product market and the total G-CSF market.^{5,27} From 2007 to 2016, the average price (expressed as price per treatment day [TD]) of a G-CSF biosimilar or reference product in the EU fell by 37%. Romania, Slovakia, and Slovenia experienced the highest reductions in total market average price, with reductions of 62%, 61%, and 57%, respectively.⁵

The price drop of G-CSF biosimilars has also led to an increase in G-CSF whole-market volume and consumption, and, subsequently, an increase in patient access. The highest changes in market volume (measured in TD, or defined daily dose) for G-CSFs when comparing

2016 volume with pre-biosimilar entrance were seen in Romania, Bulgaria, and Slovakia, with increases of 2542%, 581%, and 509%, respectively.⁵ From 2007 to 2016, patient access to biosimilar G-CSFs increased by 63%, while access to biosimilar and reference products increased by 122%. The change in total G-CSF market access increased by 58%.⁵

The introduction of biosimilars into the US G-CSF market is recent. Zarxio was the first biosimilar approved in the US market, in 2015, where it competed with Neupogen.^{10,22} Zarxio was marketed with a 15% discount in cost in comparison with Neupogen, which may have contributed to it capturing 24% of the market 4 months after its launch.^{10,28} In its 2016 fourth quarter (Q4) commercial review, Amgen reported a decrease of 43% of Neupogen net sales in the United States and decreases of 25% and 34% in worldwide unit and net sales, respectively, in comparison to 2015 Q4 sales. In the review, Amgen attributed the decline in sales to biosimilar competition from Zarxio; moreover, it was noted that the drop in sales is only expected to continue.²⁹ Additionally, in its 2017 first quarter (Q1) report, Amgen reported that Neupogen sales decreased by 31% in a year-over-year comparison, and once again attributed the decline in part to competition.³⁰

With Zarxio as the only G-CSF biosimilar approved so far in the United States and with less than 2 years on the market, it is too early to make conclusions about and quantify the exact impact biosimilars will have on the US G-CSF market, and on the pharmaceutical market in general. However, many G-CSF biosimilar products are in the pipeline that promise new competition and potential market changes. The FDA has pending applications from Mylan/Biocon, Apotex, and Coherus for biosimilars for Amgen's Neulasta; this could certainly change the future of the G-CSF market landscape.^{18,27} »

Conclusion

Biosimilars are an exciting development in the pharmaceutical industry. Although relatively new in the US market, biosimilars have been available for nearly a decade in Europe. Many data on the impact of biosimilars on the European market are available to analyze and review; nonetheless, healthcare economic analysts and policy makers must account for the vast differences between European and US markets, payers, and reimbursement systems, as well as the difficulty of extrapolating data from 2 regions with different healthcare and economic models. However, the cost savings and price reductions that biosimilars offer, as seen in the aftermath of the entry of G-CSF biosimilars into the European G-CSF market, should be taken into serious consideration. Biosimilars can be valuable implements on the route to optimizing healthcare cost savings, increasing accessibility, and, ultimately, improving patients' health and quality of life.

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