The Oncologist®

New Drug Development and Clinical Pharmacology

Regulatory and Clinical Experiences with Biosimilar Filgrastim in the U.S., the European Union, Japan, and Canada

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Filgrastim • Biosimilars • Neutropenia • Biologics • Patent • Chemotherapy

Abstract

Biosimilar filgrastims are primarily indicated for chemotherapy-induced neutropenia prevention. They are less expensive formulations of branded filgrastim, and biosimilar filgrastim was the first biosimilar oncology drug administered in European Union (EU) countries, Japan, and the U.S. Fourteen biosimilar filgrastims have been marketed in EU countries, Japan, the U.S., and Canada since 2008, 2012, 2015, and 2016, respectively. We reviewed experiences and policies for biosimilar filgrastim markets in EU countries and Japan, where uptake has been rapid, and in the U.S. and Canada, where experience is rapidly emerging. U.S. regulations for designating biosimilar interchangeability are under development, and such regulations have not been developed in most other countries. Pharmaceutical substitution is allowed for new filgrastim starts in some EU countries and in Canada, but not Japan and the U.S. In EU countries, biosimilar adoption is facilitated with favorable hospital tender offers. U.S. adoption is reportedly 24%, while the second filgrastim biosimilar is priced 30% lower than branded filgrastim and 20% lower than the first biosimilar filgrastim approved by the U.S. Food and Drug Administration. Utilization is about 60% in EU countries, where biosimilar filgrastim is marketed at a 30%–40% discount. In Japan, biosimilar filgrastim utilization is 45%, primarily because of 35% discounts negotiated by Central Insurance and hospital-only markets. Overall, biosimilar filgrastim adoption barriers are small in many EU countries and Japan and are diminishing in Canada in the U.S. Policies facilitating improved U.S. adoption of biosimilar filgrastim, based on positive experiences in EU countries and Japan, including favorable insurance coverage; larger price discount relative to reference filgrastim pricing; closing of the "rebate trap" with transparent pricing information; formal educational efforts of patients, physicians, caregivers, and providers; and allowance of pharmaceutical substitution of biosimilar versus reference filgrastim, should be considered. ***The Oncologist*** 2019;24:537–548

Implications for Practice: We reviewed experiences and policies for biosimilar filgrastims in Europe, Japan, Canada, and the U.S. Postmarketing harmonization of regulatory policies for biosimilar filgrastims has not occurred. Acceptance of biosimilar filgrastims for branded filgrastim, increasing in the U.S. and in Canada, is commonplace in Japan and Europe. In the U.S., some factors, accepted in Europe or Japan, could improve uptake, including acceptance of biosimilars as safe and

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effective; larger cost savings, decreasing "rebate traps" where pharmaceutical benefit managers support branded filgrastim, decreased use of patent litigation/challenges, and allowing pharmacists to routinely substitute biosimilar for branded filgrastim.

Introduction

Filgrastim primarily reduces severe cancer-associated neutropenia after moderate-to-high cytotoxic chemotherapy administration [1]. Filgrastim patents have expired worldwide, opening the way for biosimilar filgrastims to enter international marketplaces. Biosimilar drugs are close copies of patented biologics. Biosimilar filgrastims, less expensive formulations of reference filgrastim, are the most common biosimilar oncology drugs administered worldwide. In 2016, global filgrastim sales were $4.6 billion, the largest sales worldwide for an oncology biosimilar [2]. Although marketing of biosimilar filgrastims is hoped to decrease U.S. oncology pharmaceutical costs, as has happened in several European Union (EU) countries and in Japan, current U.S. experience with biosimilars in general and biosimilar filgrastim lags behind EU and Japanese experiences [2–4].

Biosimilar premarket regulatory policies are similar in the EU, Japan, U.S., and Canada [5]. However, significant postmarketing differences in regulatory policies are reported among seven EU countries and in the U.S. and undoubtedly will continue [6]. Barriers and facilitators of adoption of the five regulatory-approved biosimilar filgrastims have been identified in the EU, where marketing experience is the longest, as well as more recently in the U.S. [6, 7]. In EU countries with large pharmaceutical economies, several facilitators exist, including hospitals being the primary biosimilar purchasers, widespread physician education about safety and acceptability, and support for pharmacist substitution [7]. However, biosimilar filgrastim adoption is often limited in the largest EU countries, where contracting relationships between manufacturers and health authority purchasing agencies, rather than pricing per se, are the primary determinant of which filgrastim product is purchased.

As biosimilar filgrastim is the first oncology biosimilar marketed in these regions, we reviewed experiences and policies for biosimilar filgrastim markets in EU countries and Japan, where uptake has been rapid, and in the U.S. and Canada, where experience is emerging. We also propose facilitators for further improving U.S. adoption.

Materials and Methods

We identified peer-reviewed articles in PubMed and Ovid. Search terms included "filgrastim," "biosimilars," "follow-on biologics," "similar biologic products," "subsequent entry biologics," "follow-on biologic products," and "similar biologic medicinal products." The search was restricted to papers in English or Japanese published between 2005 and October 2018. Non-peer-reviewed literature was also included in this Policy Review and identified through Google search and regulatory websites. In addition, article searches of international patent litigation databases were performed (keywords: patent, filgrastim, and biosimilar).

Regulations and Experience with Biosimilars in EU Countries, Japan, the U.S., and Canada

Overall, 43, 9, 12, and 12 biosimilars are approved in the EU, Japan, the U.S., and Canada, respectively.

Biosimilar regulatory approval pathways were established in the EU, Japan, the U.S., and Canada in 2006, 2009, 2015, and 2010, respectively [8–13]. Approval requires demonstrating a high degree of similarity with the reference (innovator) biologic—comparing physiochemical and immunochemical properties, biological activity, specifications, stability, safety, and efficacy [8–13].

Biosimilar filgrastim approval required efficacy evaluation based on pharmacokinetic/pharmacodynamics (PK/PD) studies (Japan) or on clinical studies (EU, U.S., and Canada; Table 1) [14, 15]. In EU countries, between 2008 and 2014, nine filgrastim biosimilars received approvals (one was withdrawn for marketing reasons) [16–23]. In Japan, in 2012, 2013, and 2014, three biosimilar filgrastims received regulatory approval. In the U.S., the first biosimilar filgrastim was launched in 2015, and the second biosimilar filgrastim was launched in 2018 [24–26], and in the same year, Health Canada issued regulatory approval for a biosimilar filgrastim [27]. Regulatory agencies in each region authorized extrapolation to all clinical indications for which reference filgrastim had previously received approval, although reference filgrastim approvals varied regionally (Table 2) [16–23, 28–36].

Mean price discounts for all available biosimilar products range from 15% to 40% compared with reference innovators. Increased use in markets in EU countries and Japan markets has been partially attributed to economic policies incentivizing biosimilars, whereas such policies are just beginning in the U.S. [37]. More than 50% of biosimilar uptake has been observed in Germany. A large price discount for infliximab led to 90% market share. The National Institute for Health and Care Excellence recommends use of infliximab biosimilar, which was followed by a 25% decrease in infliximab with improved patient access. Canada has lagged behind EU countries in adopting biosimilars, as payers have encouraged providers to prescribe biosimilars to new starts, but switching patients is not incentivized. Canadian policy makers who negotiated with manufacturers and payers incentivized prescribing of biosimilars for new starts. Japan requires biosimilars to be priced at a 25% discount versus reference biosimilars but also does not support switching to biosimilars for patients already on reference biosimilars.

Patents

In EU countries, primary filgrastim patents expired in 2006. EU patent cases are filed in national courts—to date, none have involved reference filgrastim [15]. Patent infringement cases involving a novel long-acting filgrastim and reference long-acting peg-filgrastim concluded in the U.K. (decided for

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Table 1. Key characteristics of filgrastim biosimilars in the EU, U.S., Japan, and Canada

	Year of final regulatory advice
EU	2006
Japan	2009
U.S.	2015
Canada	2010
	Regulatory approval studies
EU	Between two and four PK/PD studies in healthy volunteers measured serum filgrastim concentration and peripheral blood peak and return to baseline CD34+ cell counts after biosimilar filgrastim administration. EMA regulations support single-arm studies with historical controls or phase III studies with concurrent controls for efficacy evaluation. Single-arm studies initially and phase III studies subsequently measured efficacy (using historical or concurrent controls, respectively). Safety was evaluated in phase I and phase III studies [16–23].
Japan	Comparative PK and efficacy studies and analytic studies supported three biosimilar filgrastim regulatory approvals [28–35]. Japan's Pharmaceuticals and Medical Devices Agency requires comparative PK/PD studies. Comparative PK/PD studies were pivotal efficacy studies for biosimilar filgrastims. Phase III safety trials were regarded only as supplementary. For Filgrastim Biosimilar 1, Japanese patients were included in one of five phase III efficacy trials, a single-arm nonrandomized trial in 104 Japanese patients with breast cancer [28, 88]. Filgrastim Biosimilar 2 approval studies included three randomized trials totaling 900 European patients with breast or lung cancer or non-Hodgkin lymphoma [31, 55–57]. Filgrastim Biosimilar 3 approval studies included one single-arm trial in 170 European patients with breast cancer [34, 35].
U.S.	Analytical, immunogenicity, PK/PD studies, and one phase III noninferiority trial supported approval. Regulations required phase III studies with concurrent controls for efficacy assessment. One safety/efficacy study of reference vs. biosimilar filgrastim, conducted in 214 European patients with breast cancer, supported approval [26]. One multi-center randomized open-label assessed the immunogenicity of multiple sc doses of filgrastim-aafi or U.S. reference filgrastim in 256 healthy volunteers, one single-center randomized open-label study multiple dose 2-way crossover study in 60 healthy subjects evaluated the area under the curve for the CD34+ count and the time to maximum observed CD34+ cell with U.S. reference or filgrastim-aafi administered as a multiple dose cross-over intravenously, and a third study single-center randomized open-label single dose, 2-way cross-over single dose study in 24 subjects compared filgrastim-aaafi and U.S. reference filgrastim with the same endpoints as in the second study. There were no comparative clinical trials in the intended population submitted in the BLA or in the published literature that tested the equivalence of filgrastim-aafi (named PF-06881893 prior to FDA approval) for a clinical efficacy endpoint.
Canada	Grastofil regulatory approval was based on analytical similarity between the proposed biosimilar and reference filgrastim, PK/PD parameter comparability in healthy volunteers, and safety data from 144 healthy volunteers in three PK/PD studies and one single-arm study evaluating 120 European patients with breast cancer receiving chemotherapy vs. historical controls [27]. These studies supported approval of the same biosimilar in the EU in 2013 [19].
	Regulatory review criteria [5]
EU	General biosimilar studies apply to all biosimilars.
Japan	PD/PK studies are used to support efficacy claims for biosimilar filgrastims.
U.S.	Biosimilar filgrastim specific. Stepwise analytic approach.
Canada	Uses a new drug pathway that is not biosimilar filgrastim specific, and also a nonstepwise approach.
	Number of marketed filgrastim biosimilars
EU	8
Japan	3
U.S.	2
Canada	1
	Regulatory review [5]
EU	Biosimilar.
Japan	Biosimilar.
U.S.	Biosimilar.
Canada	New drug pathway prior to 2016. Not biosimilar specific.
	Market approval dates
EU	2008–2014
Japan	2012, 2013, 2014
U.S.	2015
Canada	2015
	Regulatory review times, months
EU	16–20
Japan	11–13
U.S.	9
Canada	13
	Originator main patent expiration
EU	2006
Japan	2009
U.S.	2013
Canada	2024 (Canadian Federal Court ruled that composition of matter claims for filgrastim were obvious since 1985) [42–44]

(continued)

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Table 1. (continued)

	Patent litigation between reference and biosimilar sponsor
EU	None.
Japan	None.
U.S.	Multiple cases involving biosimilar and reference filgrastim manufacturers. Resolved in part for each party. Supreme Court 2017 decision removed 180-day wait period for marketing [41].
Canada	Reference filgrastim sponsor challenged biosimilar sponsor alleging that the main patent was infringed. Case dismissed at 1 month [42–44].
	Most recent biosimilar naming convention
EU	2006
Japan	2013
U.S.	2017
Canada	2012
	Naming
EU	Brand names are used for each product.
Japan	Filgrastim-1, -2, or -3 is the biosimilar name.
U.S.	Filgrastim plus four-letter suffix is the placeholder nonproprietary name (Filgrastim-sndz).
Canada	Brand name is used for the biosimilar.
	Labeling
EU	A table comparing reference and biosimilar filgrastim data is included on the biosimilar filgrastim label. Accofil and Grastofil have Black Triangles in the labels, indicating that they are biologics that received regulatory approval after 2013.
Japan	The labels of the reference and biosimilar filgrastims are the same, except that the biosimilar label has the biosimilar designation, PK/PD studies, and safety information obtained from preapproval clinical trials [28–35, 54].
U.S.	The labels for reference and biosimilar filgrastim are similar.
Canada	Biosimilar designation is included in the label, with an explanation of what a biosimilar is. The remainder of the biosimilar label is identical to the label of the reference biosimilar label.
	Guidelines
EU	2011 European Society of Medical Oncology guidelines indicate that biosimilar filgrastims are an acceptable alternative to reference filgrastim [52].
Japan	2017 JSCO guidelines indicate that biosimilars are equivalent to reference filgrastims. Biosimilar filgrastim 2 has the strongest supportive data [54].
U.S.	2016 ASCO guidelines indicate that biosimilar filgrastim is acceptable vs. reference filgrastim. Preliminary data indicate that switching is safe [53].
Canada	2016 Cancer Care Ontario guidelines do not include text on biosimilar filgrastim [59].
	Substitution
EU	EU country specific. Some countries allow and encourage pharmacy substitution for new starts. The U.K., Italy, and Spain prohibit it.
Japan	Substitution is not allowed.
U.S.	37 states have passed legislation against pharmacy substitution. Some states will allow substitution if the interchangeability has been designated by the FDA.
Canada	Encouraged by some provinces.
	Interchangeability
EU	Not addressed by the EMA. No regulatory statements from individual countries on interchangeability are in place.
Japan	No regulatory statements on this topic exist.
U.S.	Draft FDA Guidance on this topic is in the public comment phase.
Canada	No statements on filgrastim interchangeability have been made. This requirement is delegated to the individual provinces.
	Determinants of price setting
EU	Set by individual EU counties; bidding does occur at hospitals and regions. Hospitals negotiate tender offers.
Japan	Set by the Central Social Medical Insurance Council of the Ministry of Health Labor and Welfare, which consists of insurers, insured people, medical doctors, dentists, pharmacists, public members, and industries.
U.S.	Set by federal health programs and with individual health insurers. Rebates are common.
Canada	Set by provinces.

Abbreviations: ASCO, American Society of Clinical Oncology; EMA, European Medicines Agency; EU, European Union; FDA, U.S. Food and Drug Administration; JSCO, Japan Society for Clinical Oncology; PD, pharmacodynamics; PK, pharmacokinetics.

the new agent) and in Germany (decided for peg-filgrastim; Table 1). No reported patent litigation involved biosimilar and reference filgrastim [14, 38].

In Japan, the primary filgrastim patent expired in 2009 [39, 40]. Patent protection (and postmarketing exclusivity periods) prevents sponsors from using originator data in

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biosimilar applications [14, 39, 40]. Japan also discourages patent litigation [14].

Filgrastim's primary U.S. patent expired in 2013 [15, 37]. Litigation involving biosimilar filgrastim initially focused on "patent dance" provisions of the Biologic Price Competition and Innovation Act [8]. The patent dance is the legal framework for the exchange of drug-related patent information between the biosimilar applicant and the reference biologic drug sponsor. The patent dance envisaged anticipating patent disputes by encouraging biosimilar makers to share their U.S. Food and Drug Administration (FDA) application and manufacturing information with the originator's sponsor prior to approval. The manufacturer of the first FDA-approved filgrastim biosimilar declined to participate. The reference filgrastim sponsor filed a procedural challenge in Federal District Court for the Northern District of California, and the patent dance was ruled optional. This ruling was upheld by the U.S. Court of Appeals for the Federal Circuit Court. The Circuit Court also ruled that the filgrastim biosimilar sponsor requirement for a 180-day notice of intent to market was effective only *after* FDA approval [41]. In 2017, the Supreme Court ruled that biosimilar makers can provide notice of launch *before* FDA approval [41]. In 2018, Amgen filed a patent infringement complaint under the Biologics Price Competition and Innovation Act against the manufacturer of filgrastim-aafi, the second FDA-approved biosimilar filgrastim, claiming that the biosimilar maker Hospira infringed on its "997 patent." In 2017, the Federal Circuit Court affirmed the Southern District Court of Florida's finding on noninfringement of Amgen's "138 patent" by Apotex.

In Canada, filgrastim's primary patent will expire in 2024 [42]. One patent litigation case involving a biosimilar and reference filgrastim concluded in 2015 [42]. The Canadian Federal Court ruled that composition of matter claims for filgrastim were obvious since 1985 [43]. Reference filgrastim's sponsor's 2016 appeal was considered moot as biosimilar filgrastim received Canadian approval in 2015 [44]. After approval of the filgrastim biosimilar from Apotex, the manufacturer sued Amgen, the manufacturer of a branded filgrastim for damages under section 8 of the Patented Medicines Notice of Compliance of Canada (SOR/93-133) claiming unjust enrichment [45].

Naming and Labeling

Naming and labeling conventions are important because biosimilars and reference biologics do not have identical chemical characteristics. The European Medicines Agency advises biosimilar filgrastim sponsors to share International Nomenclature Names with reference filgrastim. Unique brand names are also assigned, ranging from Accofil to Zarzio (Table 1) [5, 16–23].

In Japan, biosimilar nomenclature rules were revised in 2013 [46]. Approved filgrastim biosimilars have nonproprietary names: "Filgrastim (Genetical Recombination) [Filgrastim Biosimilar X]," where X is the integer 1, 2, or 3 indicating the three different biosimilar drugs, respectively [28–35]. The brand name for reference filgrastim is "Gran," and its nonproprietary name is "Filgrastim (Genetical Recombination)." Biosimilar filgrastim product labels are similar to reference filgrastim labels [28–35]. However, labels include information on biosimilar PK/PD studies and biosimilar filgrastim safety obtained from preapproval clinical trials [28–35].

In the U.S., the first biosimilar filgrastim placeholder nonproprietary name, filgrastim-sndz, reflects the sponsor's name (Sandoz) [47]. The proprietary name is Zarxio (although it is Zarzio in EU countries) [24, 47]. In 2016, the FDA finalized a Naming Guidance, and in 2017, the FDA distributed for comment a Draft Labeling Guidance [8, 48, 49]. Distinct suffixes for each product are preferred as the best way to track biologics or biosimilars [48]. The Naming Guidance advises sponsors to attach random four-letter suffixes to a reference drug and its biosimilar and use the same base name [48]. Filgrastim-sndz does not follow this Naming Guidance because its name was developed prior to the Guidance. The second FDA-approved biosimilar, filgrastim-aafi (proprietary name Nivestym), received approval in July 2018 and is named according to the 2016 FDA Naming Guidance. Labels for the two biosimilar filgrastims and reference filgrastims are similar [24, 50].

The Canadian biosimilar filgrastim name is Grastofil, the same name as a biosimilar filgrastim marketed in Europe [19, 36]. Filgrastim prescriptions in Canadian provinces must specify "Neupogen" or "Grastofil." Labels for biosimilar and reference filgrastim in Canada are similar. Grastofil's label states that the drug is a subsequent entry biologic.

Clinical Guidelines

Clinical guidelines for biosimilar filgrastim use vary. The 2016 statement by the European Organization for the Research and Treatment of Cancer and the 2016 updated statement by the European Society of Medical Oncology consider biosimilar filgrastim an alternative to originator filgrastim [51, 52]. The 2017 statement by the Japan Society of Clinical Oncology, the 2016 American Society of Clinical Oncology (ASCO) Guideline Update, and the 2018 ASCO Statement, Biosimilars in Oncology, recommend either biosimilar or originator filgrastim for febrile neutropenia prevention [53–55]. Filgrastim Biosimilar 2 is described in Japan as having the strongest clinical evidence for biosimilar filgrastims (randomized phase III trials and a meta-analysis) [56–58]. Cancer Care Ontario 2016 Filgrastim Guidelines do not discuss biosimilars [59].

Substitution

Filgrastim substitution refers to pharmacist replacement of one filgrastim for another [5, 8]. Individual EU member states establish their own substitution policies [6]. Several EU countries encourage automatic pharmaceutical substitution for new starts [6]. There is variability within the EU countries on how to execute substitution. France, The Netherlands, and Germany permit pharmacist filgrastim biosimilar substitution for treatment-naïve patients [6]. However, pharmacists in Belgium, Italy, Norway, and the U.K. are prohibited from substituting biosimilars [6]. The 2014 Social Security and Finance Bill of France allows automatic pharmacist substitution for treatment-naïve patients—the first EU law of this

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Table 2. Currently marketed biosimilar filgrastims in European Union countries, the U.S., Japan, and Canada

Product [ref.] (cost vs. branded filgrastim)	Manufacturer	Approval date	Submission date	No. of months under review	Indications[a]
European Union					
Accofil [16] (35% discount on average)	Accord	Oct. 2014	Mar. 2013	19	1–5
Biograstim [17] (35% discount over average)	AbZ-Pharma	Sep. 2008	Jan. 2007	20	1–5
Hexal [18] (35% discount on average)	Hexal	Feb. 2009	Sep. 2007	16	1–5
Grastofil [19] (35% discount on average)	Apotex	Oct. 2013	Apr. 2012	18	1–5
Nivestim [20] (35% discount on average)	Hospira	Jun. 2010	Feb. 2009	16	1–5
Ratiograstim [21] (35% discount on average)	Ratiopharm	Sep. 2008	Jan. 2007	20	1–5
Tevagrastim [22] (35% discount on average)	Teva	Sep. 2008	Jan. 2007	20	1–5
Zarzio[b] [23] (35% discount on average)	Sandoz	Feb. 2009	Sep. 2007	16	1–5
U.S.					
Filgrastim-sndz [24] (15% discount)	Sandoz	Mar. 2015	May 2014	9	1–6
Filgrastim-aafi [25] (30% discount)	Pfizer	Jul. 2018	Sep. 2017	10	1–6
Japan					
Filgrastim Biosimilar 1 [28–30] (35% discount)	Fuji/Mochida	Nov. 2012	Dec. 2011	11	1–9
Filgrastim Biosimilar 2 [31–33] (35% discount)	Nippon Kayaku/Teva	Feb. 2013	Mar. 2012	12	1–9
Filgrastim Biosimilar 3 [34, 35] (35% discount)	Sandoz	Mar. 2014	Mar. 2013	13	1–9
Canada					
Grastofil [36] (25% discount)	Apotex	Dec. 2015	Feb. 2015	Grastofil [36] (25% discount)	Apotex

Note: The biosimilar filgrastim Grastofil manufactured by Apotex received regulatory approval in EU countries in 2013, and a similar biosimilar filgrastim from the same sponsor was approved by Health Canada in 2015. The Zarzio biosimilar filgrastim manufactured by Sandoz received regulatory approval in EU countries in 2009, a similar biosimilar filgrastim from the same sponsor was approved in Japan in 2014 (Filgrastim Biosimilar 3), and a similar biosimilar filgrastim from the same sponsor (filgrastim-sndz) received regulatory approval in the U.S. in 2015. The filgrastim biosimilar manufactured by Teva received regulatory approval in EU countries in 2008, and a similar biosimilar filgrastim (different pharmaceutical formulation; Filgrastim Biosimilar 2) received regulatory approval in Japan in 2013. One EU-approved biosimilar filgrastim was voluntarily removed from the EU market.

[a]Extrapolated indications are as follows. All approved indications are extrapolated from clinical indication 1. EU regions differ in their approved indications for biosimilar filgrastim because the reference filgrastim regulatory-approved indications vary regionally. In each region, biosimilar filgrastim received complete regulatory extrapolation.

Indication 1 is for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation who are considered to be at increased risk of prolonged severe neutropenia.

Indication 2 is for the mobilization of peripheral blood progenitor cells (U.S., Japan, and EU countries) or for mobilization of autologous peripheral blood progenitor cells in order to accelerate hematopoietic recovery after high-dose chemotherapy (Canada and the U.S.).

Indication 3 is for patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L and a history of severe or recurrent infections.

Indication 4 is for patients with persistent neutropenia (ANC $\leq 1.0 \times 10^9$/L) and a history of severe or recurrent infections.

Indication 5 is for patients with advanced HIV infection, to reduce risks of bacterial infections when other therapeutic options are inappropriate.

Indication 6 is for patients with acute myeloid leukemia receiving induction or consolidation chemotherapy: to reduce the time to neutrophil recovery and the duration of fever, after induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia.

Indication 7 is for patients with myelodysplastic syndrome and neutropenia (in Japan).

Indication 8 is for patients with aplastic anemia and neutropenia (in Japan).

Indication 9 is for healthy donors for allogeneic peripheral blood stem cell transplantation (in Japan).

[b]Biosimilar filgrastim from Sandoz has a trade name of Zarzio in Europe and Zarxio in the U.S.

Sources: Regulatory information for each product, as filed with regulatory agencies in the EU, the U.S., Japan, and Canada [16–24, 28–36]. Current Average Sales Price information for Medicare Part B Drug Average Sales Prices is at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html (accessed November 11, 2018).

type [6]. In 2015, the Dutch Medicine Board supported pharmaceutical substitution of biosimilars [60].

In Japan, nonproprietary names of biosimilar products differ from originator product. Automatic pharmacy substitution is not allowed because filgrastim product must be ordered by product name [45].

In the U.S., 35 states passed legislation allowing substitution when a biosimilar is designated medically interchangeable and if prescribers do not write "dispense as written" or "brand medically necessary" [61]. The filgrastim product must be recorded, and substitution must be communicated to prescribers [61].

In some Canadian provinces, pharmacy substitution is encouraged for new starts but not for persons already receiving reference filgrastim [62]. If a "Neupogen" prescription is written, the pharmacist must dispense branded filgrastim [63].

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Interchangeability

Medical interchangeability designation requires testing confirmation that a biosimilar is expected to achieve the same clinical effect in any given setting and in any patient who has previously received reference biologic [5, 8]. EU interchangeability policies vary by country. Biosimilar and reference filgrastims are interchangeably designated in Finland [6, 64]. In Norway, publicly funded clinical trials are evaluating interchangeability for infliximab but not filgrastim [65].

In Japan, designation criteria for medical interchangeability are not currently being developed [45]. Although physicians can prescribe biosimilar filgrastim, they are asked to consider regulatory guidelines noting that "a biosimilar product should not be substituted for or used alternately with original biologics or other biosimilar products in the same class for the same indication throughout a course of treatment in order to assure traceability of any adverse events" [12].

The U.S. is developing regulatory criteria for establishing interchangeability. The 2017 FDA Draft Biosimilar Interchangeability Guidance is in the comment phase [66]. The FDA proposes that switching studies should evaluate changes in treatment that result in two or more alternating exposures to the proposed interchangeable and to the reference product [67]. In some states, even if interchangeability is designated (after interchangeability regulatory requirements are finalized), providers or pharmacists must notify patient recipients of substitution [61]. One U.S. study with 109 patients with cancer identified no safety concerns when biosimilar and reference filgrastim were administered after alternative chemotherapy cycles [68]. Larger switching studies have not been reported.

In Canada, the authority to declare a biosimilar and reference biologic as interchangeable rests with each province and territory. There are currently no published regulatory criteria for filgrastim interchangeability designation [27, 69].

Pharmacovigilance

Effective biosimilar pharmacovigilance is difficult [70, 71]. Safety concerns arise because biosimilars are not exact copies of reference drugs. For example, 181 patients with chronic disease developed antibody-medicated pure red cell aplasia after exposure to months of administration of an epoetin formulation (a protein that is not a biosimilar) in which a manufacturing change (substitution of polysorbate 80 for albumin) had been made [72]. In 2012, five patients with chronic kidney disease died from anaphylaxis after exposure to another protein, peginesatide, a novel erythropoiesis stimulating agent that is not a biosimilar, which had been obtained from a multidose vial. Use of phenol as a stabilizer in multidose vial formulations may have contributed, because no anaphylaxis cases were observed with a single-dose peginesatide formulation that did not include the phenol stabilizer [73]. The World Health Organization's pharmacovigilance database includes more than 100 spontaneously reported adverse event reports for three biosimilar filgrastims marketed in EU countries, but no report for any person receiving biosimilar filgrastim in Japan, Canada, or the U.S. [74]. If a substitution from reference filgrastim to a biosimilar filgrastim occurs and is a suspected cause of an adverse event, the event cannot be evaluated unless product-specific information is available. Although traceability is important, spontaneous reporting systems are not considered dependable [70]. This concern supports unique biosimilar filgrastim naming [5].

Formal risk management programs for biosimilar filgrastim are required in the EU for the two recently approved biosimilar filgrastims (Grastofil and Accofil) but not for older biosimilar filgrastims [16–23]. This plan is part of a U.K.-wide Black Triangle program adopted EU-wide in 2013. Medicines with Black Triangle assignments include biologicals authorized after January 2011 [75]. The Triangle appears in patient information leaflets beginning in 2013 (the Triangle remains on the leaflet for a 5-year period). All suspected side effects associated with Black Triangle drugs should be reported (submitting a Yellow Card indicating a potential side effect) to regulators [16, 19]. In Japan, postmarketing risk management plans are necessary for all biosimilar products [45]. The U.S. and Canada do not have formal biosimilar filgrastim risk management programs [27–35, 69, 76].

Pricing and Utilization

Biosimilar filgrastim pricing and utilization differ internationally. In 2013, market penetration for biosimilar filgrastim in the five largest EU markets ranged from 35% in France to 91% in Sweden [4]. Price discounts average 35% in EU countries [4]. Price discounts, large numbers of competitors, and distribution channels characteristics reportedly do not correlate with biosimilar filgrastim uptake [77]. Tendering (i.e., bidding) at a hospital, regional, or national level in Belgium, France, Germany, Italy, Norway, and the U.K. correlated with higher biosimilar filgrastim utilization [4, 6]. Overall, filgrastim utilization and market share are empirically dependent on local and regional policy options rather than pricing [2].

In Japan, the Central Social Medical Insurance Council negotiates pricing. Biosimilar filgrastims are priced 35% less than originator filgrastim ($133 vs. $207 for a 300-microgram syringe). Biosimilar filgrastims accounted for 8%, 10%, 12%, 26%, and 46% of the filgrastim market share, annually, from 2012 to 2106 [2, 45, 78].

In the U.S., utilization of the first biosimilar filgrastim was reportedly at 24% after 4 months of marketing, whereas nationally the cost was reportedly discounted by 15% [3]. Discounts are often provided to hospitals that provide care to indigent patients; rebate agreements vary among hospitals and purchasing organizations, and payment programs differ for fee-for-service and bundled marketing models. In 2017, for the Veterans Administration, the costs of biosimilar versus reference filgrastim 300-microgram doses were $149 versus $267 (45% discount) [79]. The 2017 Average Sales Price for Medicare for biosimilar versus reference filgrastim is $219 versus $302 for a 300-microgram dose (38% discount) [80]. Interestingly, biosimilar filgrastim entered the market in 2016 at an insignificant discount, with the 2015 Average Sales Price for biosimilar versus reference filgrastim 300-microgram dose being $291 versus $300 [81]. At the University of California San Diego Medical Center, conversion from

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branded to biosimilar filgrastim resulted in $220,000 in savings (from $1.31 million to $1.09 million, a 16% discount) [82]. The mean filgrastim price reportedly decreased 11% between September 2015 (with filgrastim-sndz market entry) to the second quarter of 2016 [83]. In 2017, sales of branded filgrastim dropped precipitously by 28%. The second FDA-approved filgrastim biosimilar (filgrastim-aafi) began marketing in October 2018, reportedly with a 30% discount versus branded filgrastim (Table 2).

In Canada, biosimilar filgrastim coverage varies by province and insurer. Some private payers and government programs reimburse biosimilar filgrastim costs, and patients must pay the reimbursement difference if reference filgrastim is dispensed [63]. Ontario lists filgrastim biosimilar as a general benefit without restrictions and branded filgrastim as a limited benefit for certain indications [63]. PharmaCare British Columbia reimburses biosimilar filgrastim use if branded filgrastim has not been administered previously [84]. Reported prices are $144 versus $192 for a 300-microgram prefilled syringe of biosimilar versus reference filgrastim (25% discount) [27]. Biosimilar filgrastim uptake was initially low, possibly because of the availability of only a 300-microgram prefilled syringe. Subsequently, with a large vial size and the generalized benefit designation, adoption reportedly increased significantly.

Challenges and Recommendations

Adoption of biosimilar filgrastim is high in EU countries and Japan and is growing in Canada and in the U.S. [3, 5, 85]. Among EU countries with highest baseline filgrastim use (Germany, Italy, Spain, and the U.K.), incentive policies, including filgrastim biosimilar target expenditures, prescription minimum quotas, prescription monitoring, clinical guidelines supporting biosimilar filgrastim, pharmacist substitution, and provider biosimilar education, have reportedly facilitated uptake, whereas price discounts reportedly had little impact [77]. EU countries with hospital-based filgrastim markets adopted biosimilars rapidly, whereas EU countries with predominantly retail markets did not [77, 86]. In EU countries with low biosimilar filgrastim uptake (Romania, Bulgaria, and Slovakia), lowering prices had the most utilization impact [87]. In Japan, the Central Social Medical Insurance Council established a 35% discount for biosimilar filgrastims. In this hospital-based market, biosimilar filgrastim utilization increased steadily [45, 54]. In the U.S., challenges to adoption continue [2–5, 7, 85, 88]. These may diminish when the FDA finalizes its Draft Interchangeability Guidance (allowing pharmaceutical substitution in some states), pricing variations among hospitals and health systems decrease, physicians and patients are educated about biosimilar filgrastim safety, formularies include biosimilar filgrastim, and patent litigation processes improve (Table 3) [15, 85, 88]. Federal legislation supporting interchangeability and subsequent universal state-wide adoption of substitution would improve biosimilar adoption. Long-term registries evaluating efficacy, safety, and immunogenicity as well as switching studies as part of interchangeability designation might overcome physician and patient concerns [88]. In Canada, provincial insurers reimbursed biosimilar filgrastim as

Table 3. Recommendations for improving biosimilar filgrastim uptake in the U.S. [85, 89]

Physician-level stakeholder educational efforts, including continuing medical education courses that include information on FDA regulations for biosimilar approval, naming, labeling, extrapolation, substitution, switching, costs, safety, effectiveness, and pharmacovigilance (FDA, manufacturers, and oncology/hematology societies) and information that focuses on acknowledging behavioral economics as a concept that affects prescribing
Patient-level and caregiver-stakeholder educational efforts including FDA-supported public service announcements (FDA, manufacturers, social media, and oncology/hematology societies)
Pharmacist-level stakeholder educational efforts, including continuing pharmacist education courses (FDA, manufacturers, medical societies, Hematology-Oncology Pharmacy Association)
Payer-level stakeholder educational efforts (FDA, manufacturers, medical societies, and Hematology-Oncology Pharmacy Association)
Ensure that reference filgrastim manufacturers allow access to samples to facilitate development of new biosimilar filgrastim products via clinical evaluation (FDA)
Improved hospital, payer, pharmacy benefit manager pricing and roll-out of incentive pricing and policies for prescribers to order biosimilar filgrastim for new starts (private and public insurers)
Make biosimilar filgrastim eligible for pass-through payment status (Centers for Medicare and Medicaid Services)
Transparent pricing that diminishes the “rebate trap” and ensures that rebates focus on patient access and out-of-pocket costs, not list price (Centers for Medicare and Medicaid Services)
Finalize Guidance on Biosimilar Switching and Information needed to approve this request (FDA)
Decrease use of inter partes reviews and patent infringement lawsuits that prevent entry of new biosimilar filgrastims on the market (Federal Trade Commission can control this) [90]
Establish processes to support competitive pricing- targeting 25% to 30% discounts (Centers for Medicare and Medicaid Services and other insurers)
Promote pharmacy substitution from prescription for branded to biosimilar filgrastim for new starts if FDA has designated the biosimilar as interchangeable (State Boards of Pharmacy)
Promote pharmacy switching for persons on branded filgrastim if FDA approval of interchangeability designation has occurred and ensure that patients are aware of the switching (State Boards of Pharmacy)
Establish postmarketing safety and real-world data registries (FDA and pharmaceutical manufacturers)
Add a column to the Purple Book for filgrastim biosimilar in which reference filgrastim is also listed along with the date of exclusivity expiration, and provide references to source materials for each regulatory-approved biosimilar filgrastim product (FDA)
Allow patients to share in biosimilar cost savings through reduced out-of-pocket cost requirements (Centers for Medicare and Medicaid Services, private health insurers)
Consider publishing summary review documents for any biosimilar filgrastim product that receives regulatory approval, even if no Advisory Committee meeting is held (FDA)
Simplify coding and reimbursement processes and work with payers on demonstrating value of biosimilar filgrastims, including lowering costs and improved access

Abbreviation: FDA, U.S. Food and Drug Administration.

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a general medical benefit in 2016, diminishing financial barriers, and utilization increased [6, 33]. Among U.S. states, some EU states, and some Canadian provinces, the absence of formal interchangeability regulatory criteria presents potential barriers.

Hakim and Ross reviewed obstacles to U.S. adoption of biosimilars for chronic diseases [85]. They outlined nonallowance of automatic substitution practices in most states, reluctance to use formulary utilization management strategies to promote biosimilar use for chronic diseases, widespread rebate agreements between pharmaceutical companies, pharmacy benefit managers, and other payers creating incentives for payers to prefer more expensive branded biologics over biosimilars. Hakim and Ross proposed strategies to improve competition, lower prices, and increase biosimilar availability, including passing automatic substitution laws in all states based on interchangeability (after the Draft Guidance on Interchangeability is finalized), developing treatment guidelines from physician organizations that recommend biosimilars as first-line agents, and developing legislative initiatives focusing on how rebates influence therapeutic choice for patients. These barriers and policy recommendations are in line with empirical findings reported for biosimilar filgrastim adoption in EU countries, suggesting that they may apply equally well in the U.S. for biosimilar filgrastim.

Conclusion

We found that postmarketing international harmonization of clinical and regulatory policies for biosimilar filgrastim is not occurring and is unlikely to occur. Biosimilar filgrastim adoption in the U.S. can be fostered by a range of policies, as evidenced by positive experiences in several EU countries and Japan and by recommendations made by stakeholders for patients, providers, pharmacies, and manufacturers of reference and biosimilar biologics, by FDA commissioner Scott Gottlieb, and by several FDA employees (at the FDA's Facilitating Competition and Innovation in the Biological Products Marketplace, Part 15 Public Hearing; Table 3). Price discounting is a major facilitator in Japan, Canada, and in many EU countries. In the U.S., although biosimilar filgrastim garnered 24% market share in 4 months, several factors could further improve biosimilar filgrastim acceptability and uptake, including physician and patient acceptance of biosimilars; hospital, payer, and pharmacy benefit manager pricing that supports a 35%–40% discount as in EU countries and Japan; favorable formulary decisions supportive of biosimilar filgrastim; and substitution allowance of biosimilar filgrastim for reference filgrastim. With the entrance of a second biosimilar filgrastim into the market and FDA approval of two filgrastim products, it is likely that, going forward, price competition and cost savings will develop in the U.S., as has occurred in many European countries.

Acknowledgments

Robert C. Kane, M.D., the 2016 recipient of the Food and Drug Administration's Frances Kelsey Award for Pharmaceutical Safety Efforts, died after the submission of the first draft of this manuscript. The article is submitted in his honor.

This study was funded partly by the National Institutes of Health (grant R01CA16509), the American Cancer Society (IRG-13-043-01), the South Carolina SmartState Program, and unrestricted grants from Doris Levkoff Meddin and Frank P. and Josie M. Fletcher to the Center for Medication Safety and Efficacy of the Medical University of South Carolina and the University of South Carolina. No funds were accepted from a pharmaceutical manufacturer or a pharmaceutical distributor. The views expressed represent independent work of the authors and should not be considered to represent the views or policy of any other entity or agency.

Parts of this study were presented at the Asia Oncology Summit in Kyoto, Japan, March 3–7, 2016 (travel fees were supported by *Lancet Oncology*), and at the American Society of Hematology conference in San Diego, CA, December 1–4, 2018.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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For Further Reading:
Eduardo Cazap, Ira Jacobs, Ali McBride et al. Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust. ***The Oncologist*** 2018;23:1188–1198.

Implications for Practice:
Biosimilars of monoclonal antibody anticancer therapies are beginning to emerge, and more are likely to become available for clinical use in the near future. The extent to which biosimilars can contribute to cancer care will depend on their level of acceptance by health care systems, health care professionals, and patients. A better understanding of the regulatory basis for the approval of biosimilars may enhance confidence and trust in these agents. In order to have informed discussions about treatment choices with their patients, oncologists should familiarize themselves with the biosimilar paradigm.

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