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Review

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Biosimilars in oncology: key role of nurses in patient education

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Biosimilars have the potential to lower costs and increase patient access to life-saving cancer therapies. However, lack of familiarity with biosimilars can be a barrier to their adoption, limiting their health and economic benefits. As highly trusted healthcare providers, nurses play integral roles in patient education. This review aims to help prepare nurses to respond to potential questions from patients on biosimilars. The regulation, use and potential benefits of biosimilars are discussed, with a focus on biosimilars in oncology. Overall, biosimilars are highly regulated medicines that provide comparable benefits to available biologics. Nurses can influence the adoption of biosimilars through patient education and can impact the future of the field in their expanding roles within health care systems.

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Keywords: biologics • biosimilars • cancer care • nurse

Biologic therapies have had a tremendous impact on the treatment landscape of cancer and have revolutionized both supportive care and targeted cancer treatment [1]. However, cost and availability remain major barriers to patient access to these life-saving medications [2]. In recent years, many manufacturer exclusivity agreements for biologics have expired, leading to the emergence of a new class of therapeutics called biosimilars [3]. A biosimilar is a biologic therapy that has highly similar properties and comparable clinical efficacy and safety to an existing reference biologic [4,5]. The increasing availability of biosimilars has the potential to expand patient access to biologics and reduce the economic burden that cancer and other chronic diseases can place on patients and healthcare systems. However, lack of awareness of the efficacy, safety and regulation of biosimilars may limit their adoption [6]. To maximize the potential benefit of current and emerging biosimilars, it is critical to raise awareness of their efficacy and safety through the education of health care providers and patients.

Because of their regular interactions with patients, nurses have the opportunity to play important roles in biosimilar use, particularly regarding patient education [7,8]. Nurses are often the health care providers who administer treatments to patients, monitor patients most closely while on treatment, and spend the most time with patients and their caregivers. Furthermore, in the USA, nurses consistently represent the most trusted group of healthcare providers [9]. Therefore, they may frequently field patient questions about their medications and thus have a unique opportunity to provide necessary education. It is important that nurses understand what biosimilar medications are and how they are regulated to accurately communicate their efficacy, safety, and potential benefits to patients.

As the number of biosimilars for oncology indications increases, encouraging the adoption of biosimilar therapies through patient education is important to maximize their potential economic and health benefits. The current narrative review aims to provide oncology nurses with the information they may need to respond to questions patients may have about biosimilars. We review the production and regulation of biosimilars using the guidelines for biosimilar development from government agencies. A PubMed search was performed to identify clinical studies and review articles relevant to the importance of biosimilars and their use in oncology practice. The patient

Table 1. Summary of the regulation of biosimilars by the EMA and US FDA.

	EMA[†]	FDA[‡]
Biosimilar definition	• Biological medicinal product that contains a version of the active substance of an already authorized medicinal product in the EEA • Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise must be established	• Biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components • There are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency
Approval pathway	• Market authorization application	• 351(k) BLA
Data requirements	• Analytical • *In vitro* studies • *In vivo* animal studies (if deemed necessary) • PK and PD (when feasible) clinical studies • Clinical immunogenicity assessment • Efficacy equivalence trials • Comparative safety trials	• Analytical • *In vitro* studies • *In vivo* animal studies (required) • PK and PD clinical studies • Clinical immunogenicity assessment • Efficacy equivalence trials • Comparative safety trials
Extrapolation	• Considered in light of the totality of data (e.g., quality, nonclinical, and clinical)	• If the proposed product meets the definition of a biosimilar, the sponsor may seek approval in other indications of the reference product • Sufficient scientific justification is needed for extrapolating clinical data
Interchangeability	• Not designated by the EMA • Regulated at the national level	• Designated by the FDA based on a supplemental interchangeable application
Pharmacovigilance	• Postmarketing monitoring of clinical safety required • The risk management plan should take into consideration identified and potential risks associated with the use of the reference product and detail how these issues will be addressed • Immunogenicity should specifically be addressed in this context	• Robust postmarketing safety monitoring required, as with biologics • Plans should take into consideration any particular efficacy or safety concerns of the reference product • Rare safety risks (e.g., immunogenicity) should be evaluated

[†]Information adapted from the EMA guidelines published in 2015 [4].
[‡]Information adapted from FDA Guidance for Industry on biosimilarity, published in 2015, [5] and interchangeability, published in 2019 [23].
BLA: Biologics license application; EEA: European Economic Area; PD: Pharmacodynamics; PK: Pharmacokinetics.

questions that form the structure of the review were identified in guides developed by the European Specialist Nurses Organisation (ESNO) and the EMA on the topic of biosimilars [10,11].

Introduction to biosimilars

When patients are introduced to biosimilars, as with any new therapy, they are likely to have questions as to what they are and why they are important [12]. In this context, it may be useful to discuss how biologics are made and compare biosimilars with generic small-molecule medicines. Although biosimilars are not generics, they can potentially have similar economic benefits and increase patient access to effective but costly medications.

What are biosimilars?

Unlike small-molecule pharmaceuticals, which are chemically synthesized, biologic medicines are produced by genetically engineered cells, such as bacteria, yeast, or mammalian cells [13]. Because small-molecule drugs are synthesized chemically, different manufacturers can produce identical drugs, referred to as generics. Since biologics are produced by living organisms, and no living cell is the same, it is impossible to independently develop a molecule that is identical to an existing biologic [6]. When a manufacturer develops a product to achieve the same clinical result as an existing biologic, the new biologic product is called a biosimilar. Unlike generic medicines, biosimilars are highly similar but not equivalent to their reference biologic [4,5].

Regulatory agencies such as the EMA and the US FDA have strict guidelines in place to ensure that approved biosimilars do not differ from the reference biologic in their clinical benefits and risks to patients [4,5]. Biosimilars must undergo rigorous testing to ensure they fit within the EMA and FDA definitions of biosimilarity (Table 1). Both agencies define biosimilarity to mean that the new product exhibits properties highly similar to the reference biologic and that any small variances do not result in differences in clinical efficacy and safety. These standards are rigorously tested in a stepwise development process, described in more detail later in this review.

Why are biosimilars important in oncology?

Potential benefits of biosimilars

Biologics can be highly effective, potentially life-saving therapies for multiple conditions and have become important components of the standard of care for patients with cancer [1]. Cancer represents a large economic burden for patients and health care systems and costs countries billions of dollars each year [14]. The cost of biologics is high relative to small-molecule pharmaceuticals and can contribute significantly to the rising cost of cancer therapy [1]. Because of their cost and limited availability, biologics may be rationed, withheld until later stages of disease, or reserved for only the most severe cases, limiting patient access to optimal care [1,15].

Biosimilars have the potential to lower costs of cancer care and increase patient access to biologic therapies. Biosimilars generally have lower development and production costs compared with their reference biologics. As a result, the cost of biosimilars can be up to 30% lower than the cost of the reference biologic [6]. Biosimilars can also drive down the cost of biologics by introducing price competition to the market [2]. Lower costs could reduce the economic burden of cancer for both patients and health care systems and increase patient access to biologic therapies. This has been demonstrated in the EU, where the availability of biosimilars has resulted in payers and health care authorities relaxing restrictions on the use of biologic therapy [16].

Biosimilars in cancer care

The first marketed biosimilars included therapies for supportive care in oncology, approved in the EU over 10 years ago [15]. Filgrastim (Neupogen®; Amgen Inc, CA, USA) is a biologically active form of the cytokine granulocyte colony-stimulating factor approved to treat febrile neutropenia in at-risk patients undergoing chemotherapy [15]. The first biosimilars of filgrastim (Tevagrastim®; TEVA GmbH, Ulm, Germany and Ratiograstim®; Ratiopharm GmbH, Ulm, Germany) were approved by the EMA in 2008, and by 2014, seven biosimilars of filgrastim were available in the EU after comparative clinical trials confirmed their efficacy and safety profiles were similar to originator filgrastim [17–19]. By 2015, filgrastim biosimilars made up the majority of EU filgrastim use [15]. Biosimilars are also available for the long-lasting form of filgrastim, pegfilgrastim (Neulasta®; Amgen Inc), and as of February 2020, 13 biosimilars of filgrastim or pegfilgrastim are approved in the EU and/or the US (Supplementary Table 1).

Because of their relatively long time on the market, filgrastim biosimilars have provided evidence for the reliability of the biosimilar development and approval process. Several postmarketing studies have demonstrated that biosimilars of filgrastim offer the same efficacy in the treatment of febrile neutropenia during chemotherapy as originator filgrastim in the real world [15]. Furthermore, the availability of these biosimilars has substantially lowered costs and improved patient access to granulocyte colony-stimulating factor therapy [20]. For example, in Sweden, where biosimilars accounted for more than 80% of filgrastim use by 2013, daily filgrastim use increased up to fivefold compared with before biosimilars were available [15,16].

More recently, biosimilars for targeted cancer therapies have become available, specifically monoclonal antibodies. The introduction of monoclonal antibodies to the cancer treatment landscape has greatly improved patient outcomes for multiple cancer types [2,21]. Since 2017, monoclonal antibody biosimilars for several targeted cancer therapies have been available in the EU and the US (Supplementary Table 2) [21]. These include several biosimilars of the reference biologic trastuzumab (Herceptin®; Genentech Inc., CA, USA), used to treat HER2-overexpressing breast and metastatic gastric cancers. Several biosimilars of rituximab (Rituxan®; Genentech Inc and Biogen Inc, MA, USA); MabThera®; Roche Pharma AG, Grenzach-Wyhlen, Germany), used for the treatment of B cell lymphomas, are also available. Two biosimilars of bevacizumab (Avastin®; Genentech Inc.), used in the treatment of different solid tumors, have been approved for use in both the EU and the US. Monoclonal antibody biosimilars have the potential to greatly impact the global cost of cancer care and increase patient access to targeted biologic therapies.

Questions on biosimilar efficacy & safety

If a patient is prescribed a biosimilar, they may have concerns surrounding the extent of the similarity of this medication to the reference drug, especially regarding its efficacy and safety. Because they interact closely with patients and caregivers, nurses may have the opportunity to provide education and comfort to patients who may be unsure about their new medication. Questions on the extent of similarity of a biosimilar, including its efficacy and safety, may be addressed by describing the stepwise testing and robust evidence of biosimilarity required by regulatory agencies for approval (Table 1) [4,5]. Although the development process for a biosimilar differs from the development process and procedures required for the reference biologic (Figure 1), the EMA and FDA have

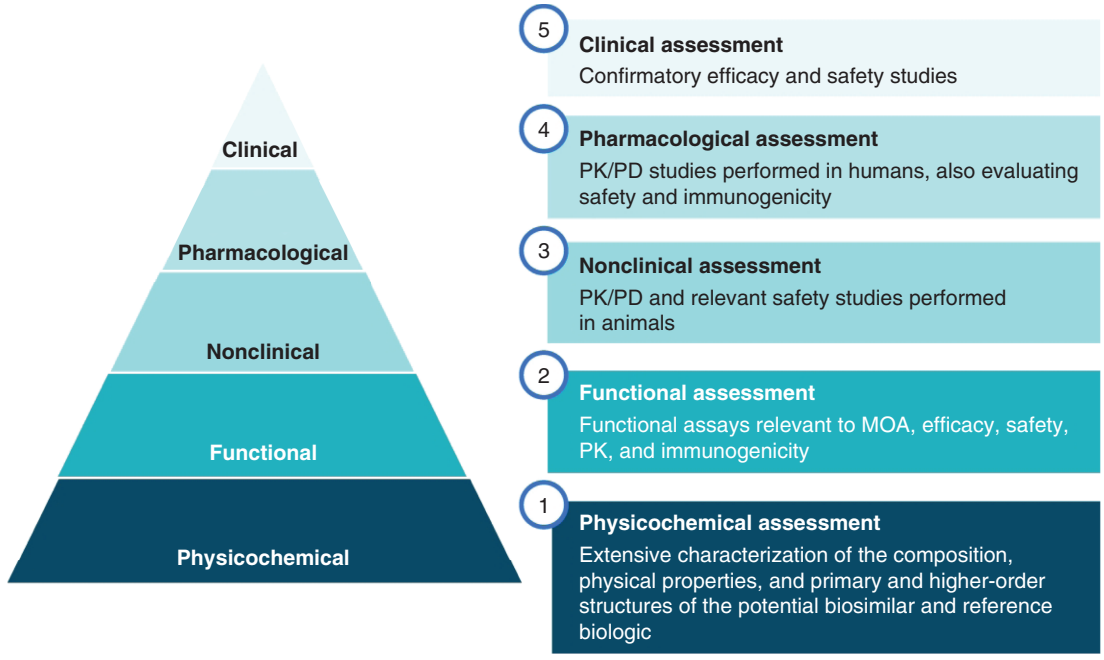

Figure 1. Stepwise assessment of biosimilars. The relative amount of data generated during each step of testing for a potential biosimilar is represented. For a biosimilar, similarity to the reference product must be established; therefore, most of the testing occurs between the physicochemical and nonclinical steps. Since efficacy and safety have been established for the reference product, clinical trials of a biosimilar are designed to efficiently compare clinical outcomes in the most sensitive patient populations.
MOA: Mechanism of action; PD: Pharmacodynamic; PK: Pharmacokinetic.

stringent guidelines to ensure that there is no difference in their clinical benefits or risks to patients [4,5]. In this section, we propose potential questions from patients regarding biosimilar efficacy and safety and summarize information on the biosimilar development and approval process, including the rationale behind the approach to biosimilar testing that may be useful to address such concerns.

What does it mean that the medicine is 'similar' to the original biologic?

Heterogeneity of biologic medicines

Several carefully controlled steps are involved in the production of biologic therapies, including biosimilars [13]. First, researchers must engineer host cells to produce the desired compound. The product must then be isolated from the cells, properly formulated, stored and transported before it is used to treat patients. Variability can be introduced at each step of this production process, and cells can behave differently in response to small variances in their environment. For these reasons, all biologics have an inherent degree of heterogeneity, and characteristics of the same biologic can change over time, even without a change in the manufacturing process. As noted above, in the case of a biosimilar, it is not possible to produce an identical biologic through an independent manufacturing process. However, to address this inherent variability, regulatory agencies require that biosimilars fall within prespecified limits of variability, with regard to their chemical and pharmacologic properties, to confirm a high degree of similarity to the reference biologic [5,22].

Preclinical & early clinical testing

Similarity of a potential biosimilar to its reference biologic is tested through comprehensive preclinical and early clinical evaluations (Table 1) [4,5]. Testing of the potential biosimilar and the reference biologic begins with structural analyses and relevant cellular functional assays. Animal studies may also be necessary to assess toxicity and pharmacologic measures of the potential biosimilar against its reference biologic. Once analytical and functional

similarity has been established, it is critical to know that a biosimilar will be processed in the human body in the same manner as the reference biologic. These pharmacologic attributes are tested through clinical pharmacokinetic and pharmacodynamic studies. These early clinical studies also assess the safety of the potential biosimilar in humans, including immunogenicity. The proposed biosimilar must demonstrate a high degree of similarity in molecular and pharmacologic attributes to its reference biologic, providing the foundation for biosimilarity.

Is a biosimilar as effective as its reference biologic?

Comparative clinical trials

Once the foundation of biosimilarity has been established in early testing, the proposed biosimilar undergoes clinical testing to assess efficacy and safety in the intended patient population. The goal of clinical testing is not to demonstrate efficacy and safety in general but to establish that there is no difference in efficacy and safety from the reference biologic [4,5]. While a newly developed biologic must undergo extensive clinical assessment to establish *de novo* efficacy and safety, clinical similarity of a biosimilar is tested in focused comparative clinical trials. These studies must be performed in a population that is both representative of the intended therapeutic population and sensitive enough for any potential differences in efficacy and safety to be detected [4,5]. Comparative efficacy trials are often based on short-term end points that have been proven to correlate with long-term efficacy. In clinical trials of trastuzumab biosimilars, pathologic complete response (defined as the absence of invasive residual tumor in the breast and lymph nodes) is used as a sensitive end point to establish biosimilarity in early breast cancer and has been strongly correlated with event-free survival [23,24]. Similarly, overall response rate is used as a sensitive end point to establish biosimilarity in metastatic breast cancer [24]. Examples of efficacy outcomes from Phase III comparative clinical trials of currently approved trastuzumab biosimilars are provided in Supplementary Table 3. Overall, comparative clinical trials are often designed to use the knowledge gained from testing of the reference biologic to confirm comparable efficacy and safety in a comprehensive but efficient manner.

Extrapolation

When biosimilarity is established in clinical trials for one indication, the biosimilar may be approved for use in other indications of the reference biologic without additional clinical testing. This process is called extrapolation [25]. Both the EMA and FDA may grant approval for extrapolated indications if scientifically justified by the evidence of biosimilarity developed in preclinical and clinical comparability studies [4,5]. For example, biosimilars of trastuzumab tested in early breast cancer were granted EMA approval across trastuzumab indications, including metastatic breast cancer and metastatic gastric cancer, based on strong evidence of biosimilarity [2]. Additionally, postmarketing studies have supported the efficacy and safety of biosimilars of filgrastim, used to treat neutropenia associated with chemotherapy, in other extrapolated indications involving stem cell mobilization [25]. Extrapolation is an important component of the approval process and can help expand patient access to biologic therapies across multiple populations with unmet clinical needs.

Is a biosimilar safe?

Pharmacovigilance

Comparable safety of a biosimilar to its reference compound is established during comparative clinical testing. Additionally, as with any medication, both the EMA and FDA require close monitoring of biosimilar safety after approval [4,5]. As with all biologics, a risk management plan that describes how adverse events will be identified and managed must be in place before a biosimilar is approved for use. Patients treated with a biosimilar should be monitored for risks associated with the reference biologic as well as any potential rare side effects that may be unique to the biosimilar.

A possible safety concern with biologics, including biosimilars, is immunogenicity, or the tendency of a medicine to elicit a potentially harmful immune response in the patient [4,5]. Several factors can contribute to immunogenicity, including nontherapeutic structural attributes of a biologic, dosing and duration of treatment, and patient characteristics (e.g., disease status and concomitant medications). For these reasons, adverse safety events related to immunogenicity may be rare and difficult to identify in initial clinical trials. Therefore, a postmarketing study or additional clinical trial may be required to evaluate immunogenicity and other potential safety concerns [5]. Postmarketing studies are part of the development program for biosimilars and can be valuable sources of real-world safety data, providing important safety information on biosimilars. For example, a postmarketing clinical trial of biosimilar filgrastim conducted in France demonstrated a safety profile similar to the initial clinical trials

Table 2. Potential patient questions and nurse responses surrounding biosimilars.

Patient question†	Potential nurse response
Is a biosimilar the same as a generic?	Because small-molecule drugs are chemically synthesized and their structure is relatively simple, equivalent copies of them can be manufactured; these copies are generics. Biologics are made by living cells and are more complex. Since no living cell is the same, it is not possible to make an identical copy of an existing biologic medicine. Biosimilars are highly similar biological products that have the same clinical efficacy and safety as an approved biologic.
We have biologic medicines; why have biosimilars?	Biologics can be highly effective treatments, but their cost limits patient access. A biosimilar medicine may be less expensive than a reference biologic because its development process is less expensive. Their introduction to the market could also lower costs through price competition. By decreasing cost and increasing availability, biosimilars can increase patient access to life-saving therapies.
Will the biosimilar medicine work as well as the original biologic?	Biosimilar medications are strictly regulated. Their approval for use depends on rigorous studies that confirm they are highly similar to the original product in terms of molecular characteristics and strict clinical testing to confirm they are equally effective.
Is this medicine safe?	To be approved for use in the clinic, biosimilars must undergo clinical testing to evaluate their safety and ensure they are not different from the reference drug. In addition, biosimilars and biologics undergo safety studies, known as pharmacovigilance, to monitor patients for unexpected safety concerns and make sure they are properly managed.
I am stable on my current treatment; why would I change?	Robust evidence supports that the biosimilar will behave in the same way as the original biologic, demonstrating that they have efficacy and safety profiles equivalent to one another. Changing to a biosimilar medicine may reduce your health care costs as well as health care system costs, increasing the viability of the system.

†Questions adapted from a communication published by the European Specialist Nurses Organisation, June 2018 [26].

and the known profile of originator filgrastim [15]. Studies such as these can increase healthcare provider and patient confidence in the safety of biosimilars and, as biosimilars are introduced to the market, could be critical in their sustainability and impact on patients and healthcare systems.

Why would my medicine change to a biosimilar?

Interchangeability

In general, interchangeability refers to the ability of a biosimilar to be used in place of its reference product. Substitution can occur when a biologic is prescribed to a patient for the first time or during a series of treatments. Regulations on interchangeability determine who must be involved in the decision to substitute a biosimilar for the reference biologic, and these regulations differ between the EU and the US.

In the US, the FDA can designate a biosimilar interchangeable after consideration of a supplemental application. A designation of interchangeable means that the biosimilar can be substituted for its reference product at the level of the pharmacy and without the intervention of the healthcare provider who prescribed the reference biologic [26]. In addition to robust evidence of biosimilarity, the FDA requires a switching study, during which the biosimilar and the reference biologic are alternated, to grant the designation of interchangeable. Overall, the FDA must conclude that the biosimilar can be expected to produce the same clinical result as the reference biologic in any patient and that the risk afforded by alternating between the use of the reference biologic and biosimilar is not greater than using the reference biologic alone [26]. Although these federal regulations are in place, the FDA had not granted the designation of interchangeable to any biosimilar as of early 2020. Therefore, the decision to prescribe a biosimilar in the US is currently made by and can be discussed with the prescribing healthcare provider.

In the EU, the EMA does not define interchangeability or designate a biosimilar as interchangeable with the reference biologic [10]. Rather, regulations regarding the substitution of biosimilars for their reference products are determined at the national level. Different countries have varying policies concerning interchangeability. Many European countries support the use of biosimilars but require the decision for a biosimilar to be substituted for the reference biologic to be directed by the health care provider [10,27]. However, with growing evidence supporting the efficacy and safety profiles of biosimilars, some countries, such as Norway, are moving toward permitting automatic substitution of biosimilars by pharmacies [27].

Conclusion

Biologics have become an important factor in the treatment and management of cancer. Biosimilars are highly regulated biologic medicines that have the potential to improve patient care by reducing the rising costs of cancer treatment and increasing patient access to innovative therapies. As more biosimilars are approved worldwide, nurses have the opportunity to play an integral role in their adoption through patient education. A summary of the patient

questions discussed herein as well as potential responses is presented in Table 2. With a thorough understanding of biosimilars, including their efficacy and safety profiles, nurses can help alleviate patient concerns and maximize potential public health benefits.

Future perspective

In the coming years, more oncology biosimilars will likely enter the market, having the potential to lower costs of cancer care and increase patient access to highly effective supportive and targeted therapies. Because of their regular close interactions with patients, nurses are in a unique position to influence the adoption of biosimilars through patient education. As patient advocates, nurses can help ensure patients have access to necessary treatments and take advantage of potential economic advantages as more biosimilars enter the market. Furthermore, as healthcare needs grow worldwide, nurses are taking on complex advanced roles within healthcare systems, both inside and outside the realm of patient care [28]. In the coming years, nurses will continue to take on increasingly active roles in research, clinical decision-making and clinical leadership. In these roles, nurses can impact the field of biosimilar development beyond patient education, including driving biosimilar development through execution of clinical trials, prescribing biosimilar therapies and educating fellow healthcare providers. As both the biosimilar and advanced nursing fields expand in the next 5–10 years, the impact of nurses on the uptake of biosimilar medicines may be an important area of future research.

Executive summary

- Biosimilars have the potential to reduce cost and expand access to important biologic therapies for supportive and targeted cancer care, but lack of familiarity with biosimilars may limit their adoption.
- As trusted healthcare providers, nurses may be in a unique position to help maximize the potential health and economic benefits of biosimilars through patient education.

Introduction to biosimilars

- Unlike generic versions of small-molecule pharmaceuticals, it is impossible to produce a molecule that is identical to an existing biologic.
- Biosimilars are medicines that are highly similar to an existing biologic and do not differ in their clinical benefits and risks to patients.
- Biologics have become standard of care for many patients with cancer; however, the cost of biologic medicines contributes to the large economic burden cancer care represents for patients and healthcare systems.
- The benefits of biosimilars have been documented in supportive cancer care, as the availability of biosimilars of filgrastim over the last 10 years has substantially lowered costs and improved patient access to therapy for chemotherapy-associated neutropenia.
- More recently, biosimilars of monoclonal antibodies for targeted cancer therapy have become available and could improve access for many patients.

Biosimilar efficacy & safety

- Biosimilars are strictly regulated by the EMA in the EU and the FDA in the US.
- For a biosimilar to enter the market, it must undergo rigorous stepwise testing to demonstrate that it is highly similar to the reference biologic and does not differ in clinical efficacy and safety.
- As with any biologic medicine, the long-term safety of a biosimilar is closely monitored after its approval through pharmacovigilance programs.

Summary

- With a thorough understanding of biosimilars, including their development, regulation and efficacy and safety profiles, nurses can help alleviate patient concerns and maximize potential benefits of biosimilars for patients and healthcare systems.
- In their expanding roles within healthcare systems, nurses have opportunities to impact the field of biosimilars beyond their role in patient education as researchers, prescribers and clinical leaders.

Author contributions

Both authors contributed to the conception of the review; the collection, analysis, and interpretation of the information within; the drafting of the review; and the critical revision of the review for important intellectual content. Both authors approve this review for submission.

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