

# Are the perspectives regarding the use of biosimilars in the setting of haematology and blood and marrow transplant changing?

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**Introduction:** Canada is among the leading spenders in pharmaceuticals. Based on projected figures, the cost of pharmaceuticals is expected to rise by another 6–12% by 2023. Approximately CAN\$4.6 billion of healthcare funding is spent on biological drugs (including growth factors and monoclonal antibodies) which are commonly used in the setting of haematology and blood and marrow transplant.

**Aim:** As healthcare funds become more scarce, a need to investigate cost-effective alternatives at both the federal and provincial levels to provide cancer care is imperative.

**Discussion:** Biosimilars, also known as ‘subsequent entry biologics’ (SEBs), are cheaper alternatives to biological drugs. Biosimilars have been utilized in many European countries for years with significant cost savings and no significant reporting of adverse events. In Canada, there is a reluctance to use biosimilars due to the potential risk of adverse effects which can occur if the biosimilar is interchanged with the originator product. In keeping with this reasoning, Alberta’s stance is against substitutability or interchangeability of biosimilars/SEBs with the reference product.

**Conclusion:** For the benefit of cost-effective, quality cancer care, it is time to re-examine the use of biosimilars in our province and understand if the potential risks outweigh the benefit of cost savings.

**Keywords:** Biologics, biosimilars, blood and marrow transplant, cost, haematology, subsequent entry biologics (SEBs)

Based on a trade agreement with the European market, Canadian drug costs are among the highest in the world, second to the US [1]. In addition, through the Comprehensive Economic Trade Agreement (CETA) with the European Union, Canadian pharmaceutical costs are expected to increase further by another 6.2–12.9% by 2023 [1]. One class of drugs which erodes our healthcare dollars is biologicals [2]. Biologicals are relatively large complex molecules [drugs] synthesized from living organisms or their products, especially a human or animal protein, such as a hormone or antitoxin, that is used as a diagnostic, preventive, or therapeutic agent [3]. Examples of biologicals include interferons, interleukins, monoclonal antibodies, growth factors, vaccines and some polypeptides [3].

The present drug expenditure on biological medicines in Canada is valued at CAN\$4.6 billion [4]. According to Betito, spending on biologicals has increased by more than 200% in less than a decade [4]. While biologicals represented only 1% of (benefit) claims in 2015, they accounted for nearly 21% of total prescription drug spending [4]. These figures are significant to provincial and Canadian healthcare systems in settings such as haematology and blood and marrow transplant where often biologicals such as filgrastim are commonly used. Although essential to many cancer treatments, biologicals are expensive treatments and pose a great burden on healthcare expenditure. The need for more cost-effective measures is imperative to healthcare systems, insurance providers, healthcare providers and patients. One cost-effective strategy is the use of biosimilars [5].

## What are biosimilars?

Biosimilars, also referred to as ‘subsequent entry biologics’ (SEBs), are not generic drugs. They are manufactured from living organisms and although similar to their originator drug, biosimilars/SEBs are not identical in composition [5, 6]. They are rigorously evaluated on a case-by-case basis prior to regulatory approval [5, 6]. Regulatory bodies provide approval based on robust comparability exercises demonstrating similarity with the originator product [5, 6]. Similarity is demonstrated on the basis of biochemical characterization, i.e. purity, chemical identity, protein structure and receptor on/off kinetics, biological activity and clinical similarity for at least one indication [5, 6]. Biosimilars/SEBs must demonstrate that the mechanism of action and the receptor involved being identical to those of the originator [6]. They are further evaluated to ensure safety, efficacy (through pharmacodynamics and pharmacokinetics testing) and cost benefit [6]. The significance of implementing the use of biosimilars in Canadian cancer care systems relates to cost savings and easier access to pharmaceuticals and treatments for Canadian cancer patients. If biosimilars are more cost-effective and are proven to be safe and equally efficacious while ensuring positive outcomes for patients, the question remains why they are not being utilized more often?

## Interchangeability of biosimilars versus the originator biological

The use of biosimilars in Canadian provinces continues to be controversial. Some of this controversy stems from the uncertainty of whether biosimilars/SEBs are considered interchangeable with the originator biological. Varying definitions of the word ‘interchangeable’ may occur in different countries and differing regulatory bodies. ‘Interchangeability’ refers to a biological product which is a biosimilar to the reference product; it is expected to produce the same clinical result as the reference product in any given patient and the risk in terms of safety and diminished efficacy of switching back and forth with the reference product, is not greater than the risk of using the reference product without any such switch occurring [7, 8]. Although Health Canada has the authority to approve the use of biosimilars on a case-by-case basis, the authority to decide whether a

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biosimilar is substitutable or interchangeable with the reference biological lies at the provincial level and differs from province to province [8]. In the US, generic medications are often interchangeable meaning they can be switched back and forth (at the pharmacy level) with the reference product during the course of a patient's treatment [7]. This can be done at a lower cost without any long-term adverse effects. However, biosimilars are not generics, they differ slightly in composition and must be deemed 'interchangeable' with their reference product via US Food and Drug Administration (FDA) approval before they can be substituted without the consent of the prescribing physician [8]. Health Canada does not deem a drug interchangeable [8]. Once again, this is a decision made at the provincial level and it is up to prescribing physicians to make this decision [8]. This is due to the fact that the composition of a biosimilar is not exactly alike as their reference product leading to a risk of an adverse effect occurring [8]. At this time, Health Canada does not support the substitutability of an SEB for a brand-name biological [9] at the pharmacy level. Alberta shares Health Canada's position and is the only province that has taken the stance against substitutability or interchangeability of biosimilars/SEBs due to the potential risk of adverse effects in the long term [9].

### The occurrence with Erythropoietin

One example why certain provinces are reluctant to use biosimilar products is the adverse effect which occurred with the biological drug erythropoietin (EPO) [8]. Erythropoietin is used to stimulate the production of red blood cells in patients with treatment induced anaemia and other chronic disorders. After almost a decade of using two different EPO's on the Canadian market, a number of patients across the country developed an antibody-mediated immune response causing pure red blood cell aplasia [8]. After further investigation it was discovered that the adverse effect occurred for only one of the EPO's on the Canadian market suggesting both EPO's were not interchangeable [8]. The purpose of this paper is not to discuss the details of the issues surrounding EPO. It is however to highlight that the concern of a similar occurrence happening with the use of a biosimilar exists in Canada at both the federal and provincial level.

Appreciably, this concern is understandable; the affordability of biological pharmaceuticals is inevitably rising and therefore other viable options need to be examined. One Canadian study reports the cost saving for the use of switching to an SEB EPO in a nephrology setting is between CAN\$35–CAN\$50 million dollars annually [10]. Furthermore, the projected cost savings between 2015–2019 are estimated to be approximately CAN\$221 million [10]. The question which remains is what is the risk of an adverse effect in the long term occurring and does this risk outweigh the benefit of cost savings?

### The impact on the use of biosimilars

The answer to this is not certain in Canada. It is well documented that biosimilars have been used in the European market for years and continue to currently be in use [10, 11]. The cost savings reported related to the use of biosimilars in different European countries is astronomically beneficial [11]. According to the European Commission, since Europe introduced biosimilars back in 2006, there have been no reports of untoward effects or unexpected adverse events compared with the originator products [12]. Biosimilar filgrastim commonly used in the setting of haematology and blood and marrow transplant is reported in the European market as leading the way when it comes to market penetration, reaching market shares as high as 60–80% across Europe [11]. Between 2008–2014, nine different versions of biosimilar filgrastim have been licensed and all but one is in use in Europe [11]. One was removed for commercial reasons [11]. One biosimilar granulocyte colony-stimulating factor (G-CSF) also known as Zarzio recently approved in the US in the setting of haematology and blood and marrow transplant is used in over 40 countries worldwide [13]. In fact,

it is considered the number one biosimilar filgrastim used globally [13]. The reluctance in healthcare providers, although slowly dissipating, still exists. In March of 2016, Health Canada approved the first SEB/biosimilar of Neupogen named Grastofil [4]. Although it is up to each provincial government to decide if they will approve the use of Grastofil and whether it can be interchangeable with the originator product, it appears at least the movement toward implementing the use of biosimilars may be slowly shifting. The impact of these decisions being made at the provincial level suggests that all Canadians may not have the same access to these pharmaceuticals, possibly delaying treatment due to economic reasons. One Alberta physician believes that biosimilars should not be interchangeable [due to safety reasons] [9]. The same physician believes a solution to this issue is that governments should add biosimilars/SEBs onto their [formulary] plans while still covering biologicals [9]. Thus, placing only biological naïve patients on biosimilars so that the risk of adverse effects in the long term is not an issue and similarly, patients who are currently on innovator biologicals would not receive biosimilars [9]. Although this may not reduce the cost of biologicals as much as it could, it may be a step in the right direction towards relieving a currently overstretched healthcare budget and achieving access for some patients in the province.

The general consensus regarding the use of biosimilars is to take baby steps. The need to examine alternatives to reducing healthcare costs demonstrates Canadian healthcare providers' commitment to fiscal responsibility whilst still ensuring safety, efficacy and quality care. Although biosimilars have been in use in the European market for 10 years and more recently in the American market (such as Zarzio), Canadian provinces continue to evaluate and re-evaluate the safety, cost benefit and general access for the public [11]. With more experience and understanding from the European and American markets, it appears that a shift in Canadian thinking (and other countries) related to the use of biosimilars may be occurring. In March 2016, Apotex launched the first biosimilar/SEB approved in Canada named Grastofil [4]. This will impact the setting of haematology and bone marrow transplant as Grastofil is a biosimilar growth factor used to treat neutropenia [4]. The decision of whether this Canadian approved biosimilar will be in the formulary in each province

is currently individualized, meaning only certain patients will have access to the biosimilar. Currently, Alberta does not support the interchangeability of SEBs/biosimilars with the originator [9]. Therefore, the benefits for haematology and blood and marrow transplant patients including lower cost, faster access to treatment and overall quality of care could be compromised if the perspective is not re-evaluated [9]. Since formulation of the pan-Canadian Pharmaceutical Alliance (pCPA) in 2010, all 13 provinces and territories including the federal government have joined as of January 2016 [14]. The pCPA strives to negotiate pharmaceutical costs at a national level and as of April 2016 have released some guiding principles through beginning policy frameworks and national processes concerning the consistent negotiations of biosimilars/SEBs in Canada [14]. The leaders of the alliance admit that much work still needs to be done before a more comprehensive policy framework can be cemented [14]. Therefore, the decisions related to the interchangeability of biosimilars with the innovator biological will remain at the provincial level. We will have to wait for each province to reveal their decision if biosimilars such as Grastofil will become formulary and how that decision will impact haematology and blood and marrow transplant patients and cancer care as a whole.

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