

Ever-Evolving landscape of biosimilars in Canada; findings and implications from a global perspective

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Siu *et al.* have comprehensively assessed the rapidly changing regulation and reimbursement environment for biologicals and biosimilars in Canada and the resultant implications.

Brian Godman, Eleonora Allocati and Evelien Moorkens review the paper by Siu *et al.* regarding the evolving regulatory and reimbursement landscape in Canada (1), and subsequently link these within the broader global context of biosimilar market access to stimulate future activities and debates in this important area. This includes the current and potential market value of biosimilars, their regulatory and reimbursement environments as well as ongoing initiatives across countries to enhance their utilisation to maximise potential savings. In addition, the potential sustainability of appreciable discounts among both originator and biosimilar manufacturers.

Siu *et al.* point out that biologics are now commonly prescribed medicines for a wide variety of disease areas including diabetes, immunological diseases such as arthritis, inflammatory bowel disease, and psoriasis, as well as for a number of cancers (1-4). Their high prices coupled with the prevalence of these diseases have resulted in considerable sales. Worldwide sales of cancer medicines, many of which are biologicals, was US\$107billion in 2015 and rising (5, 6). The global anti-TNF market was valued at US\$ 40.4 billion in 2017, and expected to expand at 2.54% per year with Europe and the US currently accounting for 87.7% of sales (7). Within this, worldwide sales of adalimumab were US\$ 17.6 billion in 2017, rising to nearly US\$ 20 billion in 2018 thereby making it the world's best selling medicine, with infliximab sales at US\$ 5.9 billion in 2017 and etanercept at US\$ 5.8 billion in 2017 (8, 9). In Canada in 2017, biologicals accounted for 21.6% of overall public healthcare expenditure with the anti-TNF medicines accounting for 8.2% of total expenditure (1). This compares with the US where biologicals currently account for 37% of net drug spending (10). In the UK, anti-TNF medicines are also one of the highest spend areas within high cost medicines, with GB£780 million spent in England in 2018 (11), and in Germany, adalimumab was the top selling medicine in 2017 with net costs to the statutory health insurance system of €975 million (12). Consequently, the introduction of biosimilars, especially in oncology and immunological diseases, should be of considerable interest to payers of healthcare and patients world-wide. We have seen limited use to date of biological medicines in many Central and Eastern European countries versus Western European countries due to their high costs and co-payments (13-15). Consequently, biosimilars should help address this as prices fall. A competitive market should also bring down the cost of biosimilar insulins, helping many patients in low and middle income countries currently denied such treatments (16).

As a result of the current and envisaged sales of biological medicines coupled with ongoing initiatives, we are seeing considerable growth in the availability and use of biosimilars especially in China and

Europe (17-20). This will help increase their world-wide sales from approximately US\$4 billion in 2018 (21). Competition, with the resultant impact on overall expenditures, should intensify as many biological medicines that are currently used first or second line in treatment regimens lose their patent benefitting patients and payers (22).

Siu *et al.* point out appreciable changes in the regulatory and HTA domains in the biosimilar environment in Canada in recent years to enhance their availability and promote their uptake (1). This includes Health Canada in 2015 launching a pilot programme to provide manufacturers with the ability to discuss their biosimilar with Health Canada. In 2017, Health Canada laid out a Regulatory Review of Drugs and Devices which included a project to improve access to biologics (biosimilars and non-biosimilars) by increasing their regulatory review capacity (1). This should result in a more secure supply of biologic drugs and more affordable biologics. In addition, Health Canada and HTA organisations in Canada as well as INESS in Quebec began collaborating in 2018 to better align review processes including biosimilars to reduce duplication and time lags between regulatory approval and reimbursement (1). Health Canada also intends to implement an updated naming convention for biologics including the product's brand name, International non-proprietary name (INN), and the Drug Identification number (DIN), to support a clear distinction between biologics including biosimilars to enhance adverse event tracking (1). There have also been initiatives in other countries to enhance earlier access to biosimilars (20, 21, 23-26) although further developments are being proposed (27). Interestingly, whilst modifications to the manufacturing process of originator biologic drugs are common, regulators have very rarely required clinical studies to assess similarities even in the case of major manufacturing changes (28, 29).

With respect to reimbursing biosimilars, a number of significant changes have taken place recently in Canada to ease the situation. In Canada, the CADTH (Canadian Agency for Drugs and Technologies in Health) Common Drug Review (CDR) plays an important role in deciding whether medicines will be eligible for public reimbursement, with the Provinces subsequently typically making the final decision based on CDR recommendations (30). In May 2019, CADTH announced that as of June 1, 2019, it would no longer routinely review biosimilars via its CDR and pCODR (pan-Canadian Oncology Drug Review) programmes to streamline access (1). A similar situation is seen in Quebec with INESS. The pan-Canadian Pharmaceutical Alliance (pCPA) subsequently uses its combined purchasing power to improve access and increase the cost-effectiveness of medicines, similar to cross country collaborations in Europe (31-34). In 2016, pCPA launched a more comprehensive biosimilar policy and in 2018 released a Biologics Policy Directive in which biologic drugs for which biosimilars are already reimbursed as well as any new biosimilar will not be considered for reimbursement unless there are transparent price reductions to the lowest list price, providing an exemplar to others (1). In addition, the potential for tiered pricing in certain therapeutic areas, which is likely to lead to increasing discounts as more biosimilars are launched. Manitoba was the first Canadian Province to instigate tiered arrangements in which biologic-naïve patients must first be prescribed a biosimilar or an approved biologic where no biosimilar exists (1). Private Insurers in Canada are also now offering preferential coverage for biosimilars leading to average savings of CAD\$8,500 per participating member per year (1). Such initiatives should help boost the use of biosimilars in Canada along with educational, awareness and other initiatives, with biosimilar use currently lagging behind Europe (1, 19).

Biosimilars Canada has also recently developed a centralised patient support service platform to assist manufacturers and patients (1). Policies regarding switching should also help enhance the use of biosimilars in Canada along with collecting real-world evidence to help allay current fears (1). There have been considerable concerns with patients being switched between an originator biological medicine and a biosimilar across countries as well as indication extrapolation especially with respect to the risk of immunogenicity-related safety issues and diminished efficacy (17, 35). However, an appreciable number of studies have now shown that such risks are unchanged when switching between an originator and a biosimilar (11, 21, 36-44). As a result, patient and physician organisations in Canada are now supporting non-medical switching (1), similar to initiatives among European countries such as France (45). The growing body of evidence for biosimilars is also leading to suggestions to modify the current lengthy approval process and costs to enhance earlier access and strengthen competition (46). There are though still concerns with switching among physicians that need to be addressed with education as these can negatively impact on their future utilisation (47-49). Additional monitoring of patient outcomes in routine clinical practice should help further reduce

possible concerns as well as potentially reduce the need for comparative clinical efficacy evidence as more originators lose their patents. This should reduce the investment needed for developing new biosimilars, and combined with developments in manufacturing (50), should help reduce future prices.

A number of other initiatives have also recently been undertaken in Canada to enhance the utilisation of biosimilars. This includes the pan-Canadian Oncology Biosimilars Initiative to enhance successful adoption of biosimilars in oncology. British Columbia launched its Biosimilars Initiative in May 2019 promoting switching, with the savings used to lower premiums and co-pays where pertinent (1). Other Provinces are likely to follow.

We have also seen initiatives among other countries to enhance the use of biosimilars. Moorkens *et al.* and Vogler *et al.* have summarised these for Europe as well as provided future guidance to further enhance their uptake (51, 52). More recently, Simoons *et al.* gave guidance on additional measures that could be introduced in Europe to fully realise the potential of biosimilars (53). We are also seeing prescribing targets for biosimilars among European countries including national frameworks (54-57). However, there are still limited initiatives in some countries including Japan where currently no position statement regarding biosimilars has been included in treatment guidelines for any of the cancer societies (58). This may change though with increasing pressure on resources and with the Japanese government now reviewing supportive measures for biosimilars (58). Smeeding *et al.* recently highlighted a number of issues that payers in the US should consider as part of any strategy to increase the use of biosimilars (59).

Ongoing initiatives across countries, including both supply-side and demand-side measures, have increased potential savings from biosimilars. Siu *et al.* suggest that by the third year of entry, potential savings from biosimilars in Canada could range from 13-43% for acute use products such as Granulocyte Colony-stimulating Factors (G-CSF) and erythropoietin (EPO) and 8-43% for chronic-use products, e.g. anti-TNFs (1). This is helped by price reductions for biosimilars in Canada ranging between 17% and 50% from the originator.

A number of European countries have introduced price-link policies for biosimilars to lower their prices and enhance savings, with other countries instigating measures such as tendering to lower prices (52, 60, 61). For instance, tendering among hospitals in Norway resulted in a 72% discount compared to its list (60), and tendering in the UK will result in GB£300million (approximately \$386 million) savings from currently GB£400 million-per-year (approximately \$514 million) spent on adalimumab (62). In Germany, the current high use of adalimumab and anticipated savings resulted in biosimilars accounting for 28% of total prescriptions of adalimumab within eight weeks of launch (12). In the US, it is estimated that biosimilars will reduce direct spending on biologic drugs by \$54 billion from 2017 to 2026 (10, 63); with savings likely to be higher with greater discounts than 20% to 30% currently seen (10). Substantial discounts for biosimilars across Europe, greater than initial considerations (61), coupled with demand-side measures, have already resulted in their appreciably increased use in recent years. In some cases and countries in Europe, biosimilars now account for the total market, e.g. EPO and G-CSF, providing guidance to others (19).

However, there are concerns that originators are starting to substantially lower their prices potentially affecting future biosimilar availability and the sustainability of the market place as seen recently with adalimumab (9, 19, 64). In addition, we are seeing originator companies defending manufacturing and other patents, as well as seeking to instigate hurdles in the US making it more difficult for insurers to place biosimilars on formularies in order to disrupt the biosimilar market (10, 65, 66). Originator companies are also developing new formulations of their biologicals to try and further disrupt the biosimilar market building on previous evergreening tactics (19, 67). There are also suggestions to lower the prices of originators in countries such as Belgium and the US over time, negating the need for biosimilars to further interfere with this market (68). We will continue to monitor these developments and their implications.

In conclusion, Siu *et al.* have provided a comprehensive review of current and planned policies in Canada to enhance the use of biosimilars at competitive prices to benefit payers and patients. This is important for disease areas such as cancer with ever increasing prices for new medicines, which potentially threaten the sustainability of healthcare systems (69, 70). It is also increasingly likely that health authorities will start re-assessing prices and potential discounts for on-patent medicines for

oncology and immunological diseases as more standard medicines used for pricing negotiations lose their patents (6, 71). Siu *et al.* also remind key stakeholders to continually monitor developments with biosimilars including both supply- and demand-side initiatives as well as encourage countries to learn from each other to enhance their uptake. This is critical for health authorities with the instigation of disruptive tactics such as in the Netherlands with AbbVie and in the US with hurdles such as rebates and other strategies with insurers to limit biosimilar use. In addition, payers need to monitor the development of new formulations by originator manufacturers and plan for the implications.

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The authors have no conflicts of interest to declare.

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