

ENVIRONMENTAL SCAN

International Policies on the Appropriate Use of Biosimilar Drugs

Service Line: Environmental Scan
Issue: 80
Publication Date: October 2018
Report Length: 22 Pages

Authors: Sirjana Pant, Louis de Léséleuc, Carolyn Spry

Cite As: International policies on the appropriate use of biosimilar drugs. Ottawa: CADTH; 2018. (Environmental scan; no. 80).

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Context

Biologic drugs are derived from the metabolism of living organisms or their cells, and are larger and more complex molecules than chemically synthesized pharmaceutical drugs. A biosimilar biologic (hereafter referred to as “biosimilar”) is a drug based on a pre-existing biologic that is itself approved for marketing in a given jurisdiction. The reference biologic is used as a biological template for the design and production of the biosimilar. Previously, biosimilars were called subsequent entry biologics in Canada. Biosimilars enter the market after the expiry of reference biologic drug patent and data protection. Biosimilars are approved for marketing after a thorough comparison with a reference drug. Given the intrinsic variability of biologic drug production systems, a biosimilar and its reference biologic drug can be shown to be similar, but not identical. In general, regulatory agencies require that the biosimilar and the reference biologic drug are similar and that there are no clinically meaningful differences in safety and efficacy between them. This is ensured using structural, functional, and human clinical studies.¹

Examples of biosimilars approved by Health Canada include Brenzys (etanercept), Erelzi (etanercept), Grastofil (filgrastim), Inflectra (infliximab), Remsima (infliximab), Basaglar (insulin glargine), Omnitrope (somatropin) and MVASi (bevacizumab). These biosimilars are indicated for various chronic conditions, including ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn’s disease, ulcerative colitis, type 1 and 2 diabetes, prevention or treatment of neutropenia, growth hormone deficiency, and various advanced cancers.^{2,3}

In 2016, the 30 top-selling biologic accounted for 24% of pharmaceutical sales in Canada. The Patented Medicine Prices Review Board (PMPRB) identified a list of 13 biologics^a — for which biosimilars have been recently launched or are expected to be launched in the next three years — that accounted for C\$3.6 billion in sales in 2016 in Canada.³ Biosimilars are regarded as cost-saving alternatives to these high-cost biologics for the treatment of various medical conditions. However, for a health care system to realize these cost savings, successful market uptake of biosimilars will depend on various factors, such as number and timing of entrants into the market, patient and health care provider’s understanding and acceptance of biosimilars versus biologics, cost of biosimilars, pricing policies, payer coverage and utilization policies, and policies around interchangeability and substitution.⁴ This Environmental Scan explores existing international policies around these factors to facilitate appropriate use of biosimilars that are proven to be safe and effective, and have the potential to reduce health care expenditures.

Biosimilars in Oncology

The oncology area makes heavy use of biologics, which leads to high and rapidly increasing costs. For example, oncology biologics bevacizumab (an antibody against vascular endothelial growth factor used in the treatment of a variety of advanced cancers), trastuzumab (an anti-HER2 used in the treatment of breast cancer), and rituximab (an anti-CD20 used in various forms of lymphomas and leukemia) were among the 30 top-selling biologics in Canada in 2016.^{3,5-8} According to a 2017 PMPRB report, the 2016 Canadian sales of the three biologics, bevacizumab, trastuzumab, and rituximab, accounted for C\$104 million, C\$180 million, and C\$241 million, respectively.⁹ Upcoming patent expiry of oncology biologics offer an opportunity to develop lower-cost biosimilars, which can limit the growing cost of oncology drug expenditure while also expanding access to these important treatment options.¹⁰ As of July 2018, there are more than 60 biosimilars in various stages of development worldwide for the three drugs: bevacizumab, trastuzumab and rituximab.¹¹⁻¹³ Further, biosimilars for some of these three oncology biologics have already received market authorization in various international jurisdictions. MVASi (reference biologic: bevacizumab) is the only oncology biosimilar approved by Health Canada.² PMPRB forecasts that biosimilars for trastuzumab

^aThese 13 biologic drugs include infliximab, adalimumab, ranibizumab, etanercept, rituximab, insulin glargine, trastuzumab, filgrastim, omalizumab, bevacizumab, epoetin alfa, natalizumab, and follitropin alfa.

and rituximab will be available in Canada between 2019 and 2021.⁹ According to the 2017 PMPRB report, the market entry of biosimilars for oncology indication could lead to significant cost saving to the Canadian health care system, depending on the market uptake, among other factors.^{9,14} However, there are concerns around the acceptance of oncology biosimilars that are used to improve survival from life-threatening diseases in a short period of time as opposed to biosimilars used in chronic conditions such as rheumatology or as supportive care in oncology.¹⁵ In addition to international post-market policy to facilitate the uptake of biosimilars, this Environmental Scan will also identify if there are any specific post-market policies for these three oncology biosimilars or if regulatory differences exist for oncology biosimilars versus non-oncology biosimilars.

Objectives

The objective of this Environmental Scan is to identify and compare international policies to facilitate the adoption of biosimilars that are proven to be safe and effective after-market authorization by the regulatory agencies. The scan will present information on biosimilar-related post-market policies in the US, Australia, New Zealand, Finland, France, Germany, the Netherlands, Norway, and the UK. This information can inform post-market policies related to biosimilars in Canada to facilitate their appropriate use. Additionally, the scan will also identify any post-market policies specific to biosimilars for bevacizumab, trastuzumab, and rituximab, as well as any regulatory differences that exist for oncology biosimilars versus non-oncology biosimilars.

The following questions are addressed:

1. What post-market policies, program, or other strategies have been established internationally to guide the adoption of biosimilars and to promote their appropriate and cost-effective use?
2. Compared with other biosimilars, are biosimilars used for the treatment of cancer (bevacizumab, trastuzumab, rituximab) associated with different pre- and post-market policies internationally?

This scan will provide information on policies established by public payers (e.g., public drug programs, medical insurers, or cancer agencies) and regulatory colleges for health care professionals. Some pre-market policies, that is, those established by regulatory agencies (e.g., policies on interchangeability in the US) can influence post-market uptake; hence, information on some regulatory policies will also be presented but will be limited to only those policies that influence post-market uptake. Other policies of interest include reimbursement frameworks, including coverage or funding mechanisms and criteria; post-market policies on interchangeability, substitutability, pricing, tendering, and prescribing (e.g., tiering, switching); and any other policy mechanisms, including specific programs and initiatives.

The Environmental Scan excludes regulatory policies and health technology assessment processes regarding biosimilars. Readers are referred to the CADTH Environmental Scan *Biosimilars – Regulatory, Health Technology Assessment, Reimbursement Trends, and Market Outlook*,³ published in January 2018, for a comprehensive overview of regulatory frameworks, health technology assessment processes, and reimbursement trends of national and international organizations, as well as a synopsis of the market outlook of biosimilars and their reference products in Canada. However, any regulatory policies that are unique to oncology biosimilars as opposed to reference biologics and non-oncology biosimilars will be explored in this scan. It should be noted that this scan excludes Canadian policies and is focused on relevant international policies only.

Methods

A limited literature search was conducted using the following bibliographic databases: Ovid MEDLINE, Ovid Embase, PubMed, and the Cochrane Library (2018, Issue 7). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>) as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English- and French-language documents published between January 1, 2013, and August 17, 2018. Regular alerts updated the search until project completion. These searches were supplemented by reviewing the bibliographies of key papers and through contact with stakeholders.

Limitations

The findings of the Environmental Scan are based on a limited literature search and may not provide a comprehensive picture of the topic. Therefore, results should be viewed as examples taken from the international setting for consideration by Canadian policy-makers. Policies on biosimilars are rapidly evolving, and in particular, biosimilars for the three oncology biologics of interest, bevacizumab, trastuzumab, and rituximab, have only recently entered the market (since 2017). Hence, new policies may rapidly emerge for these three drugs, in particular, and the details within the scan are current up to the dates indicated throughout the report.

Findings

The following section present information on post-market related policies established in the US, Australia, New Zealand, Finland, France, Germany, the Netherlands, Norway, and the UK to facilitate the appropriate use of biosimilars. Post-market policies identified in this scan apply to biosimilars in general, and limited information on policies specifically related to the three oncology biosimilars was identified.

Interchangeability, Switching, and Substitution

Switching refers to a physician deciding to exchange one medicine with another with the same therapeutic intent. Interchangeability refers to two medical treatments that are therapeutically equivalent and can be safely exchanged in clinical practice, and to the action of replacing a reference product with a biosimilar or vice versa, or replacing one biosimilar with another. Substitution is a practice of replacing one drug for another at the pharmacy level, after the physician has written a prescription. Automatic substitution refers to replacing one drug with another at the pharmacy level, without consulting the prescribers.¹⁶⁻¹⁸ Policies such as automatic substitution, interchangeability designation, and encouraging switching to biosimilars can significantly drive the uptake of biosimilars and enhance the confidence of health care professionals in biosimilars. Table 1 provides a summary of policies related to interchangeability, switching, and substitution, and lists countries where they exist.

Table 1: Summary of Policies Related to Interchangeability, Switching, and Substitution

Policies Related to Interchangeability, Switching, and Substitution	Countries Where These Policies Exist
"Interchangeability" designation for a biosimilar approved by the regulatory agency	<ul style="list-style-type: none"> US^a
Market exclusivity (for a limited period of time) for the first interchangeable designated biosimilar	<ul style="list-style-type: none"> US^a
Automatic substitution allowed for biosimilars Note: Some condition may apply (e.g., automatic substitution may be prohibited by the physician) and policy may only apply to specific biosimilars only	<ul style="list-style-type: none"> US ("interchangeable" designated biosimilars only)^a Germany ("bioidentical" biosimilars only) France (for "treatment-naive" patients only) Australia ("a-flag" designated biosimilars only)
Authorities recommend prescribing biosimilars for treatment-naive patients	<ul style="list-style-type: none"> Germany Norway France Netherlands Australia
(Physician-led) switching is encouraged for patient already treated with a reference biologic	<ul style="list-style-type: none"> Germany France Norway Finland Australia

^aAs of September 2018, none of the biosimilars approved by the FDA have received an interchangeable designation.¹⁹⁻²¹

United States

In the US, a physician can switch a reference biologic with an FDA-approved biosimilar.²² Interchangeability is a regulatory standard in the US. In 2017, the FDA released draft guidance on biosimilar interchangeability entitled *Considerations in Demonstrating Interchangeability With a Reference Product*. The FDA approves an "interchangeable" designation for a biosimilar after data, in addition to those required for biosimilarity, demonstrate that a biosimilar product can be expected to produce the same clinical result as the reference product in any given patient."²³ Further, under Section 351(k)(6) of the Public Health Service Act, the FDA will not grant interchangeability status for any second biosimilar drug until "1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product."^{16,24,25} This essentially guarantees a one year market exclusivity to the first biosimilar approved by the FDA, as an "interchangeable biosimilar" for a given reference biologic. As of September 2018, all of the biosimilars approved by the FDA were approved as a biosimilar but none have been approved as an interchangeable product, including the two oncology biosimilars, Ogrivi and Mvasi.¹⁹⁻²¹

A biosimilar approved as an "interchangeable" product by the FDA may be automatically substituted for the reference product at the pharmacy level without consulting the prescriber. However, substitution (at the pharmacy level) depends on the pharmacy practice and laws at the state level, and varies from state to state in the US.²⁶ As of April 2018, 41 states in the US have established standards on substituting biosimilars for the original reference products, whereby substitution is allowed if a biosimilar is designated interchangeable by the FDA; and eight additional states are considering such substitution laws for biosimilars.²⁷ Almost all of the 41 states allow substitution of a reference biologic with an FDA-designated interchangeable product, unless the prescriber has indicated that no such substitution be made. Depending on the state, there may be additional requirements when such substitution with an FDA-designated interchangeable biosimilar is made, including informing the physician (in majority of the states) or the patient about the substitution, retaining pharmacy records, maintaining a current list of the interchangeable drugs, or selecting the lowest priced drugs.¹⁹

Europe

As opposed to the FDA, the European Medicines Agency's (EMA) scientific review of biosimilars and market authorization does not include decision on interchangeability. As such, the EMA does not make decisions on whether the reference medicine can be switched or substituted (automatic) with the biosimilar. These decisions on interchangeability, switching, and (automatic) substitution are made at the national level.¹⁸

United Kingdom

Medicines and Healthcare Regulatory Agency, National Health Service (NHS) England, and NHS Scotland recommend that a reference drug or biosimilar be prescribed by brand name; and interchanging at the pharmacy level (automatic substitution) is not recommended. However, both NHS England and NHS Scotland advise that switching between a reference product and its biosimilar, or among biosimilars, be managed at the discretion of the prescriber in collaboration with the patient, and with appropriate monitoring in place.^{28,29}

Germany

The Paul Ehrlich^b Institute (a German federal agency) encourages prescriber-led switching.^{16,17} Use of biosimilar is encouraged for both treatment-naïve patients and those who previously received the originator molecule.³⁰ Prescribers are expected to inform patients on copayment options when they choose between a biosimilar and its reference product.³¹

Germany publishes a list of biosimilars, known as “bioidenticals,” that can be substituted at the pharmacy level, unless the prescriber specifically prohibits substitution. These “bioidenticals” refer to only those biosimilars to a reference biologic that are manufactured by the same manufacturer under the same manufacturing process, but sold under different trade names. Hence, even with the same active ingredient, some biosimilars are considered interchangeable at the pharmacy level (for automatic substitution), while others are not.^{16,17}

France

According to a ministerial directive issued in August 2017, a biological medicinal product can be switched with a similar biological medicinal product at any time during the treatment in France. Further, a prescription of a biosimilar does not require any obligation other than those required for a biologic medication, in terms of patient information and traceability of the prescription.³²

A new legislation was introduced in 2017 (Article 96 of the 2017 French Social Security Financing law) that permits biosimilar substitution, however, conditions apply. Substitution is only permitted if the patient is molecule-naïve (that is, undergoing treatment with the molecule for the first time), and that the prescribing physician has not explicitly prohibited substitution. Further, the biosimilar should belong to the same group as the prescribed product (similar biologic group). Upon such substitution, the pharmacist must inform the prescribing physician, automatic substitution is not permitted. Further substitution to another biosimilar is not permitted, and treatment continuity with the same biosimilar must be ensured. Given that there is no legal decree to implement the law, the practice of substitution is not yet taking place.^{16,17,31}

Netherlands

The Medicine Evaluation Board of the Netherland permits new patients to be treated with biosimilars right away. The Medicine Evaluation Board also permits switching between reference biologics and biosimilars, and between biosimilars (based on same reference product), but under certain conditions. As such, adequate clinical monitoring must be performed, the patient must be well informed, and detailed

^bThe Paul-Ehrlich-Institut is an agency of the German Federal Ministry of Health. Its research and control activities promote the quality, efficacy, and safety of biological medicinal products.

product and batch information of the medicine must be recorded in the patient file to guarantee the traceability of the product in the event of problems.³³ Decision on switching is led by the physician, along with the involvement of the pharmacist and the patient; and automatic substitution at the pharmacy is prohibited.^{17,33}

Norway

The Norwegian Medicines Agency (NoMA) considers that it is safe to switch between reference products and biosimilars and among biosimilars (based on the same reference product) during ongoing treatment. The decision on switching is led by the physician or the hospital, and the patient must be adequately informed. Any adverse events must be reported along with the drug name, active substance, and batch number to ensure traceability. NoMA recommends switching to achieve competition, and thus reduce the financial burden of expensive biological drugs in the health care system.³⁴

Automatic substitution at pharmacy is not allowed. However, NoMA has proposed that the Pharmacy Act (related to the automatic generic substitution in pharmacies based on the national preapproved substitution list) should be amended to include reference biologics and biosimilars for automatic substitution.^{31,34}

Finland

Finnish Medicines Agency considers EMA-approved biosimilars to be interchangeable with their reference biologics as long as the change is under the supervision of a health care professional, and that switching is documented (including brand name and batch number) as with any biological products.³⁵ Automatic substitution is not permitted in Finland.¹⁷

Australia

Encouraging biosimilar prescribing for treatment-naive patients is government policy in Australia. Physicians in Australia are also allowed to switch patients to biosimilar even if they have previously taken a reference biologic or a different biosimilar. The choice for the medicine to be used for treatment is made by the physician in discussion with the patient.^{36,37}

The reference biologic and their biosimilars are listed in the (F2) formulary under the same therapeutic group. However, this listing does not suggest interchangeability or automatic substitution. Australia's Pharmaceutical Benefits Advisory Committee (PBAC) determines interchangeability for biosimilars (and other drugs) on a case-by-case basis and those that are deemed interchangeable are given "a-flag." Automatic substitution at pharmacy level is only permitted for biosimilars that have been given this designation. Biosimilars for etanercept (Brenzys), infliximab (Inflectra), Amgevita (adalimumab) and Bioepis (adalimumab) have received "a-flag" designation, and can be automatically substituted. However, substitution is not permitted if the physician ticks the box "brand substitution not permitted," even if a medicine is designated interchangeable by PBAC.^{31,36-38}

New Zealand

New Zealand's Medicines and Medical Device Safety Authority recommends that the decision to switch a patient to a biosimilar remain at the discretion of the treating clinician, and that the patient should be informed of any risk associated with switching. Substitution is not permitted.³⁹

Supply Side Policies

Supply side policies refer to policies implemented by payers, and policies related to pricing and procurement. Payer policies typically refer to listing of biosimilars in formularies and related reimbursement policies. In terms of procurement, tendering is used to encourage voluntary price concession by manufactures and rewards low-price offers with volume and uptake. Tendering is a contracting process in which the purchaser requests various drug suppliers to submit confidential bids to supply a particular drug at a given price.¹⁶ Some countries may prohibit or limit (through price mark-up adjustments “to imitate the discounts that pharmacies receive from manufacturers for the supply of their drug” or clawback arrangements “that take a portion of the profits generated by pharmacists to account for fluctuating discounts and profit margins”) manufacturer (of both reference biologics and biosimilars) discounts offered to individual retail pharmacies, as biosimilar manufacturers are often unable to match the discounts offered by the manufacturer of the reference drug, and such discounts often limit the proportions of substitution.¹⁶ Table 2 provides a summary of supply side policies, and lists countries where they exist.

Table 2: Summary of Supply Side Policies

Supply Side Policies	Countries Where These Policies Exist	
Pricing policy	<ul style="list-style-type: none"> Free pricing 	<ul style="list-style-type: none"> US UK (but subjected to PPRS rule)
	<ul style="list-style-type: none"> Price of reference drug and biosimilars is the same 	<ul style="list-style-type: none"> Germany Norway
	<ul style="list-style-type: none"> Direct price controls (e.g., mandatory discounts) 	<ul style="list-style-type: none"> France Norway (stepped price discount over time and increase in number of competitors) Finland Australia
Procurement policy	<ul style="list-style-type: none"> Tendering at hospital, regional, and national level 	<ul style="list-style-type: none"> UK Germany France Norway Netherlands
	<ul style="list-style-type: none"> Rebates 	<ul style="list-style-type: none"> Germany
	<ul style="list-style-type: none"> Quotas 	<ul style="list-style-type: none"> Germany (for SHI)
Prohibit or limit discounts offered to individual retail pharmacies	<ul style="list-style-type: none"> Prohibit or limit discounts offered to individual retail pharmacies 	<ul style="list-style-type: none"> Germany France (restriction on level of discount offered) Norway
	<ul style="list-style-type: none"> Price mark-up adjustments 	<ul style="list-style-type: none"> UK Netherlands
	<ul style="list-style-type: none"> Clawback arrangements 	<ul style="list-style-type: none"> UK Germany Netherlands
Pharmacy policies	<ul style="list-style-type: none"> Regressive mark-up to encourage dispensing of lower-cost drugs 	<ul style="list-style-type: none"> France Norway
	<ul style="list-style-type: none"> Pharmacist are allowed to keep the difference when dispensing medicine cheaper than the reimbursement price 	<ul style="list-style-type: none"> Australia

PPRS = Pharmaceutical Price Regulation Scheme; SHI = Statutory Health Insurance.

United States

Manufacturers are free to set the price of biosimilars in the US.¹⁶ However, biosimilars could be launched with discounts. For example, Zarxio (filgrastim) and Inflectra (infliximab) were launched at a 15% discount from their respective reference products.^{40,41}

Reimbursement policies for public payers in the US such as those instituted by Centers for Medicare & Medicaid Services (CMS) were identified. Payers use reference pricing for the reimbursement of medicines.¹⁶ In principle, manufacturers are discouraged from setting a price above the reimbursement level because patients are less likely to opt for a drug with a high copayment.¹⁶ Medicare Part B (the medical component of Medicare) provides payments to physicians and hospital clinics for outpatient services such as oncology biologics.⁴⁴² In November 2017, the CMS announced changes to Medicare Part B reimbursement policies for biosimilars, for the Medicare Physician Fee Schedule and the Hospital Outpatient Prospective Payment System. This change was aimed at increasing provider and patient choice, licensing of more biosimilar products, and driving competition, among others. Previously, all biosimilars with the same reference product were classified in the same Healthcare Common Procedural System code, and payment of the biosimilars under Medicare Part B was based on products' average sales price (ASP) for all biosimilars included within the same Healthcare Common Procedural System code.⁴³ This policy did not include the ASP of the reference biologic in the weighted ASP of the biosimilars, effectively resulting in a price disadvantage for biosimilars.⁴⁴ With the November 2017 changes, beginning 2018, CMS has established "a unique code for each biosimilar product; and instead of calculating a single blended payment rate, CMS will calculate a payment rate specific to each biosimilar product (that is, payment will be based on the sum of 100 percent of the biosimilar's ASP plus 6 percent of the reference biologic's ASP). In addition, for qualifying biosimilars, instead of considering only the first biosimilar product for the reference product for Hospital Outpatient Prospective Payment System pass-through payment status, each biosimilar will be eligible."⁴³

Some private payers in the US have reimbursed biosimilars in anticipation of significant cost saving. For example, CVS health announced in 2017 that it will replace Neupogen (filgrastim) with its biosimilar (Zarxio), and replace Lantus (insulin glargine) with a biosimilar, Basaglar, on the formulary.⁴⁵

United Kingdom

Manufacturers are free to set the price of biosimilars in the UK for ambulatory care. However, biosimilars are subjected to Pharmaceutical Price Regulation Scheme rule, which sets price ceilings on the basis of negotiations and manufacturer profit levels.^{16,31}

Tendering is used to make NHS procurement decisions, where lowest price is one of the prominent factors to award the tender, which can favour biosimilars.⁴⁶ Hospital level and outpatient level tendering have both been reported, and these can cover either a whole therapeutic area or a group of drugs with the same active ingredient, or both.^{17,46} In England, tenders are held at regional level and lead to framework agreements in the four NHS regions in England, which then inform local prescribing decisions. Scotland, Wales, and Northern Ireland are also reported to have country-level tender mechanisms for biologics.³¹ In England, different commissioners reimburse medical product based on their therapeutic class. As such, biosimilars of cancer drugs are reimbursed by the NHS.⁴⁷

Further to limit any manufacturer discounts offered (mostly by manufacturers of reference biologics), the UK "adjust their price mark-ups to imitate the discounts that pharmacies receive from manufacturers for the supply of their drug" and "have clawback arrangements that take a portion of the profits generated by pharmacists to account for fluctuating discounts and profit margins."¹⁶

Germany

Manufacturers are free to set the price of biosimilars in Germany for ambulatory care but the cost cannot be higher than the reference biologic. However, individual health insurance funds (SHI) can negotiate discounts through tenders. Major discounts (e.g., 40% for infliximab biosimilar) have been reported.^{17,31}

Germany has internal reference pricing in place, and can apply therapeutic reference pricing or generic reference pricing. The reference pricing is periodically revised.^{46,48} Tenders in Germany operate in outpatient setting and are managed by the SHI.⁴⁶ Additionally, rebates have been reported for some biosimilars to reduce the net price to SHI for infliximab, epoetins, filgrastim, and somatotropins, although at varying levels.³¹ SHI also have state-level biosimilar quotas.⁴⁹

In Germany, patients have to pay the difference between the retail price and the reference reimbursement price; ultimately giving the patient incentive to choose the cheaper drug.^{46,49} Germany does not permit manufacturer discounting to retail pharmacies, and have “clawback arrangements that take a portion of the profits generated by pharmacists to account for fluctuating discounts and profit margins.”¹⁶

France

Prices of biosimilars are negotiated between the pharmaceutical companies and the Economic Committee for Medicinal Products. There is a compulsory price discount on biosimilars ranging between 10% and 20% of the reference biologic.^{16,17,46} This is dependent on various factors, including the drug’s improvement in medical benefit (Amélioration du Service Medical Rendu, ASMR) rating versus therapeutic equivalents (biosimilars are given an Amélioration du Service Medical Rendu rating of V, meaning no clinical improvement), the price of the drug in the rest of Europe, and sales volume forecasts. Further, tendering is used by hospitals, and price is one of the key factors driving procurement and reimbursement.^{17,31}

France uses a regressive mark-up system at retail pharmacy level, offering larger percentage mark-ups on cheaper drugs that are expected to provide an incentive for pharmacists to dispense low-cost drugs. There are restrictions on the level of discounts offered by manufacturers to retail pharmacies.¹⁶

Netherlands

The Netherlands also uses a fixed reference pricing system to set the price of biosimilars; that is, the price of the biosimilar is officially the same as the price of the reference product.^{16,17} Tendering is used by insurers to negotiate further discounts.^{16,50}

In terms of reimbursement, insurance companies may sometimes enforce a limitation in the prescription of the original medicinal product once the biosimilar has entered the market.¹⁷

To further limit manufacturer discounts offered to retail pharmacies (mostly by manufacturers of reference biologics), the Netherlands “adjust their price mark-ups to imitate the discounts that pharmacies receive from manufacturers for the supply of their drug” and “have clawback arrangements that take a portion of the profits generated by pharmacists to account for fluctuating discounts and profit margins.”¹⁶

Norway

In Norway, the supplier decides the price of the biosimilar; however, the price cannot be higher than the price of the reference.¹⁷ Further, a progressive or stepped price discount model is applied to the price of the biosimilar; that is, an initial price discount is set for a biosimilar that increases with time and number of competitors.¹⁶

Norway has a system of national tendering (for all products paid by the hospitals and some for outpatient use), managed by the Norwegian Hospital Procurement Trust, Division Pharmaceuticals (*legemiddelinnkjøpssamarbeid*, LIS). This tendering system has resulted in large discounts (e.g., 69% discount of biosimilar infliximab on the originator medicinal product in 2015, and a 60% discount in 2016). Following the tender, LIS ranks products based on their price, and physicians have to follow this ranking when prescribing. This has resulted in an improved market share of biosimilars (e.g., biosimilar infliximab and etanercept reached a market share above 95%, and above 82%, respectively).¹⁷ Through the procurement policies and system, the Norwegian government has replaced biologics with biosimilars as the official choice of medication in indications like rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.³¹

Norway uses a regressive mark-up system at the retail pharmacy level, offering larger percentage mark-ups on cheaper drugs, which are expected to provide an incentive for pharmacists to dispense low-cost drugs. Norway also prohibits discounts offered by manufacturers to retail pharmacies.¹⁶

Finland

Manufacturers must set the price of biosimilars lower than that of the reference product in Finland. The wholesale price of the first reimbursable biosimilar must be at least 30% lower than the approved wholesale price of the reference biologic. Price of the reference biologics are re-examined once a biosimilar is launched in the market.¹⁷

Australia

Beginning in October 2018, a mandatory reduction of 25% (increased from 16%) is applied to all government-subsidized prices for all brands of a biological medicine when its first biosimilar is listed.³⁷

Pharmacists in Australia are allowed to keep the difference when dispensing medicines cheaper than the reimbursement price. Given that some biosimilars are now a-flagged (automatic substitution allowed), the provision may provide an indirect incentive to dispense the cheaper biosimilars.³¹

New Zealand

No specific policies were identified.

Prescribing Incentives

Prescribing quotas and targets may be implemented to encourage prescribing of a specific group of drugs. Positive (gain sharing) or negative (penalties) incentives may be associated with these prescribing policies. Further, related authorities may also require physicians to prescribe from a specific list of drugs. Policies on switching (as discussed above) may also influence prescribing practices. Table 3 provides a summary of prescribing incentives, and lists countries where they exist.

Table 3: Summary of Prescribing Incentives

Prescribing Incentives	Countries Where These Policies Exist
Monetary incentive for prescribing “best value” medicine	<ul style="list-style-type: none"> • US • UK
Gain-sharing agreement	<ul style="list-style-type: none"> • UK • Germany
Pharmaceutical budget limit for clinics	<ul style="list-style-type: none"> • UK • Germany
Penalties for exceeding pharmaceutical budget limit	<ul style="list-style-type: none"> • Germany
Prescribing quotas	<ul style="list-style-type: none"> • Germany • France
Mandatory prescribing of tender-winning drugs or cheaper options	<ul style="list-style-type: none"> • Norway • Finland

United States

Specific biosimilar-related prescribing and dispensing incentives were not identified in the US. However, reimbursement policies (as discussed previously) may have a positive influence on the prescribing and dispensing of biosimilars. For example, with the new Medicare Part B reimbursement rules, physicians have an indirect incentive to prescribe the biosimilar because the lower manufacturer sales price of the biosimilar is considered into the weighted ASP paid by a physician, thus increasing the margin on the lower-priced biosimilar and decreasing the margin on the reference product.^{31,43}

United Kingdom

To ensure faster adoption of best value medicines, including biosimilars, NHS England adopted the Commissioning for Quality and Innovation scheme (GE3 Hospital Medicine Optimization) to incentivize biosimilar uptake. Providers who adopt 90% best value generic / biologic products in new patients within one-quarter of guidance being available; and 80% in existing patients, within one year of the of guidance being available receive an incentive of 1% of contract value for tariff-excluded high-cost drugs. As of March 2018, biosimilars for etanercept (Benepali, Erelzi) and rituximab (Rixathon, Truximab) are included in the list of these “best value generic/biologic.”⁵¹

Local Clinical Commissioners Groups (CCGs) have entered gain share agreements with providers, allowing them to keep a percentage of the cost savings achieved by prescribing lower-cost medicines. For example, the South West London Medicines Optimization group introduced a gain share arrangement (subject to achieving minimum targets) for biosimilars, including rituximab. This gain share arrangement for rituximab operated for 12 months following the launch of the first biosimilar version (May 2017 to April 30, 2018). The gain share arrangement aimed to incentivize early uptake of biosimilar versions and maximize savings for the local health economy.⁵² Furthermore, clinics have pharmaceutical budget limits that may encourage prescribers to choose the least expensive drugs, which in most cases are biosimilars.³¹

Germany

Initiatives such as gain sharing at physician level (that is, splitting the cost savings achieved through prescribing lower-cost drugs between the payer and prescriber) and prescribing quotas (set as a percentage of total defined daily dose, either as a maximum for an originator or a minimum for a generic or biosimilar) have been introduced for some biosimilars. Gain-sharing arrangements are established at the payer level. For example, physician association KV Westfalen-Lippe and the SHI Barmer GEK have a contract where any cost saving realized by primarily prescribing infliximab biosimilar for patients with ulcerative colitis or Crohn’s disease will be equally split between the treating physician and Barmer GEK. Quotas are

established at national level for each Kassenärztliche Vereinigungen (Associations of Statutory Health Insurance Physicians) region in Germany and local administrators can set additional targets. Country-wide biosimilar prescription quotas have been introduced for infliximab and etanercept.^{17,31} For example, in 2013, the epoetin prescription quota system for outpatient dialysis centres ranged from 18% to 60% of total prescribed volume, depending on district.¹⁶

Germany also has a state-level pharmaceutical budget at the clinic level, and their prescription patterns are monitored, giving an indirect incentive to prescribe low-cost biosimilars. Should the physician exceed the budget by 15%, they receive a written notice to reconsider their prescribing practices. Physicians exceeding 125% of their budget need to repay the amount above 115% unless it can be justified.^{16,31,49}

France

Specific prescribing and dispensing policies were not identified for biosimilars in France. However, in 2016, physicians were encouraged to prescribe at least 20% insulin glargine biosimilars in ambulatory care, providing specific supplementary remuneration based on attaining public health objectives (*rémunération sur objectifs de santé publique*).¹⁷ No other physician quotas related to biosimilars were identified. The decision to prescribe a biosimilar is dependent on whether it is listed in the hospital formulary. Through gain-sharing arrangements between hospitals and Social Security, and limited hospital budgets, hospitals are encouraged to take up biosimilars.³¹ Further, a ministerial framework was issued in August 2017 to promote widespread adoption of biosimilars. Instructions specify that 70% of the relevant outpatient prescriptions should be for biosimilars instead of reference biologics. Implementation of this policy is expected to start in 2018, including setting up new contracts with hospitals.^{31,32}

Netherlands

No specific policies were identified.

Norway

Prescribing policies in Norway are incorporated in pricing and reimbursement mechanisms. For example, all products paid by the hospitals (also some for outpatient use) are subject to tendering by the LIS. Drugs are ranked based on price and a recommendation is written. Physicians have to follow this ranking and use the cheapest drugs (often a biosimilar) unless there is a clinical reason to not use the cheapest product.^{16,31}

Finland

According to a 2017 Market Review report published by the Biosimilar Medicines Group's Market Access Committee, there is a decree in Finland that mandates physicians to prescribe the least expensive products if comparable products are available of a biological medicine, unless there is a medical justification.⁵³

Australia

In 2017, the Government of Australia reached an agreement with Medicines Australia, the Generic and Biosimilar Medicines Association and the Pharmacy Guild of Australia to promote the uptake of biosimilars by "encouraging prescribing of a biosimilar brand rather than the reference biological brand for treatment naïve patients; and providing for a simpler and faster approval process for prescribing biosimilar brands (e.g., streamlined authority) while maintaining an existing higher level authority requirement for the reference biological brand (e.g., written authority)."³⁷ However, prescribers, in consultation with the patients, will still retain the ability to decide which brand to prescribe. Required evidence to implement these uptake drivers will be considered by PBAC on a case-by-case basis; and a decision will be made on the recommendation by minister or departmental delegate based on PBAC recommendation.³⁷ These uptake drivers have been applied to infliximab, follitropin, and etanercept.⁵⁴

New Zealand

No specific policies were identified.

Initiatives to Promote the Use of Biosimilars and Improve Their Understanding

The following section presents information on initiatives at the national or organizational level that aim to improve the understanding about, build confidence in, and encourage the uptake of biosimilars.

United States

In October 2017, the FDA announced the Biosimilars Education and Outreach Campaign to increase health care professionals' knowledge and understanding of biosimilars.⁵⁵ The FDA publishes the "Purple Book," which lists biological products, including any biosimilar and interchangeable biological products, licensed by the FDA under the Public Health Service Act.⁵⁶ In July 2018, the FDA also released its Biosimilars Action Plan. The plan aims to "continue providing critical education to health care professionals, including releasing a series of videos that explain key concepts about biosimilar and interchangeable products."⁵⁷ Several resources and information materials are currently housed in the FDA website.⁵⁸

In February 2016, the Biosimilars Forum (a non-profit organization) launched an initiative, Partnership for Biosimilars Education and Access, to raise awareness and encourage access to biosimilars in the US. As a part of the initiative, the forum released two educational guides for health care professionals, media, and patient advocacy groups.^{31,59}

European Medicines Agency

Since 2017, the EMA has published various information materials as part of its ongoing collaboration to improve understanding of biosimilars across the European Union, including animated video for patients, a biosimilar guide for health care professionals, and questions and answers on biosimilars for patients.⁶⁰

United Kingdom

In 2017, NHS England published a document, *Commissioning framework for biological medicines (including biosimilar medicines)*, in which it encouraged NHS CCGs to work collaboratively with all relevant stakeholders, including the Regional Medicines Optimisation Committees, to identify the optimum approach to make the most of biosimilars. The document also presents case studies on how various CCGs have optimized the safe and effective use of biosimilars while realizing savings for local health economy.⁴⁷ By making biosimilar medicines more quickly available, the NHS aims to save up to £300 million by 2021; funds that can be redirected to providing access to other life-saving and life-enhancing treatments.⁶¹ In 2015, NHS England, the Medicines and Healthcare Regulatory Agency, the National Institute for Health and Care Excellence, the Royal Pharmaceutical Society, and industry associations published a biosimilar guide, *What is a Biosimilar Medicine? This guideline aimed to provide stakeholders with information on how to "support the safe, effective and consistent use of all biological medicines, including biosimilar medicines, to the benefit of patients."*²⁸

In the UK, hospitals published success stories of savings realized through the use of biosimilars, in an effort to improve their awareness and uptake.¹⁶ Similarly, NHS uses a presentation series to share real-life examples of using biosimilars.³¹ Furthermore, drug-specific clinical practice guidelines that can also facilitate the appropriate use of biosimilars have been published in the UK. For example, the British Society of Gastroenterology released a guideline on the use of the infliximab biosimilar for the treatment of inflammatory bowel disease.⁶²

To improve the awareness of biosimilars and to improve their uptake, industry associations as well as health care professional associations have made several efforts. For example, the British Oncology Pharmacy Association published a guideline entitled “Implementation of Biosimilar MABs in Oncology - Role of Pharmacy,” along with their position statements.⁶³

In 2016, the British Generic Manufacturers Association formed a biosimilar expert sector group, British Biosimilars Association. This industry expert group partners “with patients’ representatives, health care professionals, regulators and payers to increase understanding and to drive a sustainable environment for the development, production and continuing optimized use of biosimilar medicines across the UK.”^{31,64}

Germany

There are education programs and publications on biosimilars directed at physicians in Germany. The SHI and regional physicians’ associations hold discussions, organize educational campaigns, and publish doctor letters to build the trust in biosimilars among physicians and to inform them about the potential savings through the wider uptake of biosimilars.^{16,31,46}

France

In its recent health strategy (Stratégie nationale de santé 2018-2022), France seeks to promote biosimilar drugs that have the same efficacy, quality, and safety as the biological reference medicinal product, with the aim of achieving 80% penetration of biosimilars in their reference market by 2022.⁶⁵ This is reported to be a 10% increase on last year’s target numbers.^{32,66}

The France Foundation (a provider of education for physicians and pharmacist) has been providing biosimilars educational resources and delivering related educational initiatives for nearly 14,500 clinicians in various clinical disciplines.^{67,68}

In 2017, the National Agency for Medicines and Health Products Safety released the French biosimilar register (*liste de référence des groupes biologiques similaires*). This register is aimed at increasing physician awareness of the available biosimilar versions of reference biologics. Among other biosimilars, the list (updated on August 24, 2018) includes biosimilars for rituximab (Blitzima, Ritemvia, Rituzena, Rixathon, Riximyo, and Truxima), trastuzumab (Herzuma and Ontruzant), and bevacizumab (Mvasi). Additional information on each product (e.g., dosage, pharmaceutical form, therapeutic indications, marketing authorization holder) is also available.^{31,69,70}

Netherlands

Health authorities in the Netherlands organize scientific sessions to educate stakeholders and encourage the use of biosimilars.¹⁷

Norway

The Norwegian Hospital Procurement Trust, Division Pharmaceuticals also plans educational events for health care professionals (e.g., seminars for hospitals, lectures etc.) on the topic of biosimilars, which coincide with the presentation of the results of the tenders.¹⁷

The Health Ministry in Norway funded the NOR-SWITCH study (physician-led) to study the safety of switching from originator infliximab to its biosimilar version, CT-P13.^{16,17}

Finland

No specific initiatives were identified.

Australia

In May 2015, Australia's Department of Health announced the Biosimilar Awareness Initiative (as a part of the Pharmaceutical Benefits Scheme Access and Sustainability Package) "to support awareness of, and confidence in, the use of biosimilar medicines for health care professionals and consumers."⁷¹ The government also awarded a \$5 million grant to GBMA Education Limited (to be completed up to December 2020) to undertake activities to complement and extend the department's Biosimilar Awareness Initiative, which is to promote the appropriate prescribing, dispensing, and use of biosimilar medicines. To further support the initiative, the Australian government is implementing two specific biosimilar uptake drivers (as discussed in the Prescribing Policies section) to encourage the use of biosimilar medicines.⁷¹

New Zealand

No specific initiatives were identified.

Policies Specific to Biosimilars for the Treatment of Cancer

No pre- or post-market policies specific to oncology biosimilars as a therapeutic class were identified for any of the countries. However, it is noteworthy that in 2012, the EMA adopted a guideline on biosimilar monoclonal antibodies (mAb), *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*. The guideline provides information on the non-clinical and clinical requirements for monoclonal antibody-containing medicinal products claimed to be similar to an already authorized, and similar biological medicinal products (biosimilars).⁷² Recognizing the challenges in establishing similar clinical efficacy and safety of a biosimilar and reference mAb in the anticancer setting, the guideline acknowledges that surrogate end points such as overall response rate or change in tumour mass may be more appropriate. Challenges include difficulties in establishing preferred end points for confirming efficacy, such as progression-free, disease-free, and overall survival, as they may be influenced by factors such as tumour burden, performance status, previous therapy, and unrelated to differences between the biosimilar and reference mAb.⁷³

Conclusion

Biosimilars are regarded as cost-saving alternatives to high-cost biologics for the treatment of various medical conditions. Successful market uptake of biosimilars, and subsequent cost saving will depend on various factors, such as number and timing of entrants into the market, patient and provider's understanding and acceptance of biosimilars versus biologics, cost of biosimilars, pricing policies, payer coverage and utilization policies, and policies around interchangeability and substitution. This Environmental Scan explores existing international post-market policies around these factors to facilitate appropriate use of biosimilars. Biologics are also heavily used in the oncology space, leading to high and rapidly increasing costs. There are currently three oncology biosimilars that are expected to enter the Canadian market in the next three years: bevacizumab, trastuzumab and rituximab. This scan also explored any pre- or post-market policies that may be specific to biosimilars used in the treatment of cancer. However, the post-market policies identified in this scan are applied to biosimilars in general, and limited information on policies related specifically to the three oncology biosimilars was identified.

In all of the countries, physician-led switching is allowed, and some countries (e.g., Germany, Norway, France, and Australia) encourage use of biosimilars for treatment-naïve patients as well as allow switching patients already undergoing treatment with a reference biologic. In many US states, automatic substitution is permitted for biosimilars that are deemed interchangeable by the FDA, unless the physician prohibits such substitution. Other countries included in the scan do not permit automatic substitution, except for Australia and Germany, which allow substitution for a select list of biosimilars, unless the physician forbids it.

Manufacturers are free to set the price in the US, Germany, and the UK. A free pricing policy without exceeding the price of the reference product is found in Norway; officially pricing the biosimilar the same as the reference product is found in the Netherlands. Reference drug price is used to set the reimbursement price of biosimilars in the US (CMS). Tendering at the national, regional, or hospital level is used to further drive down the cost of the biosimilars in Germany, the UK, France, Norway, and the Netherlands. Finland and France have a mandatory price reduction for biosimilars.

Pharmacists are also encouraged to dispense low-cost biosimilars (when applicable) through regressive mark-up systems at retail pharmacy level, offering larger percentage mark-ups on cheaper drugs (France and Norway), or by allowing them to keep the difference between the cost of the dispensed drug and the reimbursement price (Australia). Some countries (e.g., the UK, Germany, France, the Netherlands, and Norway) may prohibit or limit (through price mark-up adjustments or clawback arrangements) manufacturer discounts offered to individual retail pharmacies, as biosimilar manufacturers are often unable to match the discounts offered by the manufacturer of the reference drug, and such discounts often limit the proportion of substitution. In Germany, patients have to pay the difference between the retail price and the reference reimbursement price, which gives the patient incentive to choose the cheaper drug.

Gain-sharing agreements to encourage physicians to prescribe biosimilars were found in the UK and Germany. SHI in Germany also has both physician and state-level biosimilar quotas. Clinics in the UK and Germany have limited budgets on pharmaceuticals, encouraging them to prescribe low-cost biosimilars. Physicians in Germany can be penalized for exceeding these budgets. Positive incentive arrangements are offered to UK physicians who adopt best value medicines, including biosimilars.

Some reimbursement policies give physicians an indirect incentive to prescribe biosimilars. For example, the new US Medicare Part B reimbursement rules, and physicians' mandatory use of the drug ranking developed by the Norwegian Hospital Procurement Trust, Division Pharmaceuticals (based on tendering and drug price).

Several other educational and awareness initiatives have been identified at the national or organization level in most of the countries studied. These initiatives are geared toward raising awareness and encouraging the use of and access to biosimilars.

Overall, this Environmental Scan identified a range of policies and initiatives that have been proposed and implemented in international jurisdictions to promote biosimilar use through various complementary levers. No policy was identified that focused specifically on oncology biosimilars, although the vast majority of policies reported here are meant to include biosimilars for all indications, including cancer treatment. Whether similar policy mechanisms can be applied in the Canadian setting will depend on a complex interplay of factors and the coordinated engagement of a number of stakeholders.

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