CADTH

ENVIRONMENTAL SCAN

Biosimilars — Regulatory, Health Technology Assessment, Reimbursement Trends, and Market Outlook

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Context

A biosimilar is a new, highly similar version of a biologic drug that comes to the market after the patent for the original product (reference product) has expired. Biosimilars were previously called subsequent entry biologics (SEBs) in Canada. Biologic drugs are a class of drugs derived through the metabolism of living organisms, rather than being synthesized by chemical reactions.[1]

The high cost of biologic drugs has created a demand for biosimilars as a cost-saving alternative. For example, in 2015 the cost of biologic disease-modifying antirheumatic drugs accounted for 10.3% of the Canadian pharmaceutical market.[2] A review by the Patented Medicine Price Review Board (PMPRB) indicated that the median discounts for biosimilars relative to reference products ranged from 13% to 34% in OECD (Organisation for Economic Co-operation and Development) countries. However, PMPRB also reported that in Canada, the list prices for the reference products are markedly higher than in many other OECD countries.[3]

The European Medicines Agency (EMA) has been the global leader in the number of biosimilar market authorizations, having authorized 28 biosimilars as of July 2017 (Table 1). Health Canada has authorized seven biosimilars and the US FDA has authorized five biosimilars. In addition, several biosimilars are currently under review by regulatory agencies (e.g., insulin glargine, pegfilgrastim, bevacizumab and trastuzumab), and more are anticipated to enter the market within the next several years.[4,5]

In Europe, the availability of lower priced biosimilars has been reported to reduce the average list prices of reference products as well as prices of products within the whole therapeutic class.[6] The extent by which biosimilar competition has an impact on price as well as volume and market share appears to vary considerably between biosimilar drugs, therapeutic areas, and European countries. It should also be noted that assessing the impact of biosimilar competition is limited by confidential discounting and rebates that occur especially in hospitals and in countries using tenders for biologic drug procurement.

The uptake of biosimilars and the potential for cost savings depends on several factors and strategies that can vary between different countries and continents. These include patent protection, regulatory requirements, health technology assessment (HTA) and reimbursement processes, procurement and tendering processes, and positions on interchangeability, substitution, and switching.[7,8] In addition, the pharmaceutical industry uses a variety of strategies, such as extending patents, product evergreening (e.g., introducing a new formulation for reference product), and rebate agreements to mitigate the decline in revenue after the patent expiration of reference products.[9,10] The pharmaceutical industry also provides a wide range of tools and services to support the use of biologic drugs and disease management.[11] Examples of the tools and services provided include clinic and product delivery supports, access to medications, education, adherence resources, and outcomes monitoring and reporting.

A recent biosimilar forum by the Institute of Health Economics (IHE) concluded that a more coordinated, disease-specific, strategic approach with identified leadership and processes to promote healthy biosimilar competition should be established in Canada.[11] To assist in establishing a suitable strategy for biologic and biosimilar use in Canada, this Environmental Scan will review the regulatory frameworks, HTA processes, and reimbursement trends for biosimilars in Canada and internationally, as well as describe the market outlook of biosimilars and their reference products in Canada.

Table 1: Biosimilars Authorized by EMA, Health Canada, and FDA (as of June 2017)

Product	Active Substance	Marketing Authorization Holder	EMA (authorization date: DD/MM/YEAR)	Health Canada (first NOC date)	FDA (date of licensure)
Amgevita / Amjevita	adalimumab	Amgen	22/03/2017		09/23/2016
Solymbic	adalimumab	Amgen	22/03/2017		
Imraldi	adalimumab	Samsung Bioepis	23/06/2017 (CHMP)[a]		
Inhixa	enoxaparin sodium	Techdow	15/09/2016		
Thorinane	enoxaparin sodium	Pharmathen	15/09/2016		
Abseamed	epoetin alfa	Medice Arzneimittel Pütter	28/08/2007		
Binocrit	epoetin alfa	Sandoz	28/08/2007		
Epoetin Alfa Hexal	epoetin alfa	Hexal	28/08/2007		
Retacrit	epoetin zeta	Hospira	18/12/2007		
Silapo	epoetin zeta	Stada Arzneimittel	18/12/2007		
Benepali/Brenzys	etanercept	Samsung Bioepis	14/01/2016	31/08/2016	
Erelzi	etanercept	Sandoz	21/04/2017 (CHMP)[a]	06/04/2017	30/08/2016
Accofil	filgrastim	Accord Healthcare	18/09/2014		
Filgrastim Hexal	filgrastim	Hexal	06/02/2009		
Grastofil	filgrastim	Apotex	18/10/2013	12/07/2015	
Nivestim	filgrastim	Hospira	08/06/2010		
Ratiograstim	filgrastim	Ratiopharm	15/09/2008		
Tevagrastim	filgrastim	Teva	15/09/2008		
Zarzio	filgrastim	Sandoz	06/02/2009		06/03/2015
Bemfola	follitropin alfa	Gedeon Richter	27/03/2014		
Ovaleap	follitropin alfa	Teva Pharma	27/09/2013		
Flixabi	infliximab	Samsung Bioepis	26/05/2016		
Inflectra	infliximab	Hospira	10/09/2013	15/01/2014	04/05/2016
Remsima	infliximab	Celltrion	10/09/2013	15/01/2014	
Renflexis	infliximab	Merck			21/04/2017
Abasaglar/Basaglar	insulin glargine	Eli Lilly	09/09/2014	01/09/2015	
Lusduna	insulin glargine	Merck	04/01/2017		
Insulin lispro Sanofi	Insulin lispro	Sanofi	18/5/2017 (CHMP)[a]		
Truxima	rituximab	Celltrion	17/02/2017		
Tuxella	rituximab	Celltrion	18/5/2017 (CHMP)[a]		
Blitzima	rituximab	Celltrion	18/5/2017 (CHMP)[a]		
Ritemvia	rituximab	Celltrion	18/5/2017 (CHMP)[a]		
Rixathon	rituximab	Sandoz	21/04/2017 (CHMP)[a]		
Riximyo	rituximab	Sandoz	21/04/2017 (CHMP)[a]		

Product	Active Substance	Marketing Authorization Holder	EMA (authorization date: DD/MM/YEAR)	Health Canada (first NOC date)	FDA (date of licensure)
Omnitrope	somatropin	Sandoz	12/04/2006	20/04/2009	
Movymia	teriparatide	STADA Arzneimittel	11/01/2017		
Terrosa	teriparatide	Gedeon Richter	04/01/2017		

CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; NOC = Notice of Compliance.

[a] CHMP has given a positive recommendation and market authorization is pending a decision by the European Commission.

Source: EMA,[4,12-15] Health Canada,[5,16] FDA.[17]

Objectives

The objective of this Environmental Scan is to identify and compare information regarding the regulatory frameworks, HTA processes, and reimbursement trends of national and international organizations and to provide a synopsis of the market outlook of biosimilars and their reference products in Canada.

The following questions are addressed:

- Regulatory Frameworks/Guidance:
  - What are the regulatory requirements for biosimilars in Canada, the US, Europe, Australia, and New Zealand?
- HTA Process:
  - How are biosimilars currently reviewed by HTA organizations in Canada, Europe (Finland, France, Germany, Netherlands, Norway, UK), Australia, and New Zealand?
- Reimbursement Frameworks:
  - What pricing and reimbursement approaches are used in Canada and internationally for biosimilars?
- Canadian Market Information:
  - Which biosimilars are currently marketed in Canada?
  - Which biosimilar products are expected to enter the Canadian market in the next three to five years?
  - Of the biosimilars currently marketed or expected to enter the Canadian market, have the biosimilars' reference product been reviewed by CADTH's CDR or pCODR, and is the reference product currently reimbursed by public drug plans and cancer agencies?

Methods

The findings of this Environmental Scan are based on a limited literature search and correspondence with key informants from selected HTA organizations. A limited literature search was conducted using key resources, including MEDLINE, Embase, and PubMed (for in process records), selected grey literature sites from the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), and through a focused Internet search. The literature search was completed on May 9, 2017.

An email survey was sent to the key informants from the following HTA organizations: Canada (CADTH, INESSS), Australia (PBAC), New Zealand (PHARMAC), Finland (The Pharmaceuticals Pricing Board and Fimea), France (HAS), Germany (IQWiG), Netherlands (ZIN), Norway (NoMa), and the UK (NICE, SMC). See Appendix A for the survey questions. The surveys were collected until August 8, 2017. All organizations responded to the survey. The key informants were asked to validate the information reflecting their responses about their respective HTA processes.

Information on federal and provincial drug program funding for biosimilars and selected reference products were collected from online formularies.[18] A representative from each drug plan was then asked to validate the information reported for their drug plan.

Regulatory Frameworks

This section briefly summarizes the key features of biosimilar development and regulatory frameworks available from selected regulatory agencies: Health Canada, US FDA, European Medicines Agency (EMA), Therapeutic Goods Administration (TGA) in Australia, and Medsafe in New Zealand.

The non-clinical and clinical regulatory requirements for biosimilar market authorization differ from the regulatory requirements for originator biologic drugs and for generic drugs. The aim of biosimilar development is to demonstrate that the biosimilar and its reference product are highly similar in terms of structure, biological activity, efficacy, safety and immunogenicity profile.[19] For biosimilars, the weight of evidence for authorization is provided by comparative quality studies that demonstrate a high degree of structural and functional similarity between the biosimilar and the reference product. The degree of similarity at the quality level determines the scope and the breadth of the required non-clinical and clinical data.[19]

In contrast to an originator drug, where the purpose of the clinical program is to independently establish safety and efficacy, the objective of clinical studies for a biosimilar is to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product. The clinical program for a biosimilar is designed to complement the structural and functional quality studies and address potential areas of residual uncertainty.[19]

Generic drugs are usually produced by chemical synthesis, and are typically smaller molecules that are easier to characterize. In contrast to biosimilars, generic medicines require a demonstration of bioequivalence. Bioequivalence is established "*when two medicines release the same active substance into the body at the same rate and to the same extent under similar conditions*."[20]

The regulators in Canada, the US, Europe, Australia, and New Zealand all follow similar scientific principles for the authorization of biosimilars. The organization applying for market authorization must provide evidence showing that the biosimilar and the reference product

are similar and that there are no clinically meaningful differences in safety and efficacy between the two products. The development of a biosimilar is based on head-to-head comparisons of a biosimilar and its reference product and it follows a step wise approach (Table 2). The development begins with studies on product quality, followed by non-clinical and clinical studies (as applicable). At each step, the developer must evaluate how much uncertainty about the similarity of the biosimilar and the reference product remains. This residual uncertainty contributes to the determination of the type and amount of data needed in subsequent steps to demonstrate biosimilarity. Decisions on biosimilar authorization are based on all of the evidence provided in the marketing application, including data derived from comparative quality, non-clinical, and clinical studies.

Table 2: Steps in Biosimilar Development[20]

Step 1	Comparative quality studies • Complete side-by-side structural and functional characterization of the biosimilar and the reference product
Step 2	Comparative non-clinical studies • Pharmacodynamic • Toxicology
Step 3	Comparative clinical studies • Pharmacokinetic/pharmacodynamics • Efficacy + safety + immunogenicity

Biosimilar guidelines

Health Canada, EMA, and the FDA all have their own guidelines and submission requirements for biosimilars.[19,21,22] Medsafe in New Zealand and the Therapeutic Goods Administration in Australia have adopted EMA guidelines.[23,24]

The EMA has overarching biosimilar guidelines that outline the quality, non-clinical, and clinical data requirements specific to biosimilar drugs. These guidelines are supplemented by eight product class–specific guidelines (e.g., a guideline for biological medicinal products containing monoclonal antibodies) and other guidelines relevant for biosimilar evaluation including immunogenicity and comparability guidelines.[21] In addition, the EMA and the European Commission have published an information guide for health care professionals that summarizes the science and regulation underpinning the use of biosimilar medicines.[20]

Health Canada and the FDA have not published product class–specific guidelines, but they also rely on case-by-case approach for biosimilar approval. Health Canada has published a guidance document on "Information and Submission Requirements for Biosimilar Biologic Drugs."[19] Health Canada has also published a fact sheet on biosimilars.[1]

The US Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product.[25] The FDA has issued a number of guidance documents for industry that outline the scientific, quality, and clinical considerations for demonstrating biosimilarity.[22] The FDA has also released a draft guidance on considerations for demonstrating interchangeability with a reference product.[26]

Definition of biosimilar and reference product

According to Health Canada, "a biosimilar is a biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug." The Health Canada definition for the reference product is: "a reference biologic drug is a biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which a biosimilar is compared to demonstrate similarity."[19]

The definitions used by other regulatory authorities are reported in Appendix B. In general, the definitions are similar between regulators. All regulators state that the reference product should be authorized in their own jurisdictions. If a reference product that is not licensed in the jurisdiction is used in the comparative studies, the sponsor must establish that it is representative of the version of the reference product authorized in the jurisdiction.

Data requirements for biosimilars

A high-level overview of product quality, non-clinical, and clinical studies is described in Table 3. For biosimilars, the weight of evidence is provided by quality (structural and functional) studies. The degree of similarity at the quality level determines the type and amount of non-clinical and clinical data needed to demonstrate biosimilarity. The non-clinical and clinical programs are designed to complement the structural and functional studies and address potential areas of residual uncertainty. The purpose of the clinical program is to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product.

Table 3: Overview of Data Requirements for Comparative Quality, Non-Clinical, and Clinical Studies that Support the Approval of a Biosimilar Drug

Product Quality[19,27,28]

For biosimilars, the weight of evidence for authorization is provided by quality studies. A biosimilar, as any other drug product, must have acceptable product quality. However, in addition to a typical chemistry and manufacturing quality data package that is submitted for an originator drug, biosimilar submissions also include extensive comparative quality data demonstrating structural and functional similarity with the reference product.

Quality studies include a complete side-by-side structural and functional comparison of the biosimilar and the reference product, including:

- physiochemical properties, including primary, secondary, and tertiary structure
- biological activity
- immunochemical properties
- purity and impurity profiles
- stability
- forced degradation profiles.

The biosimilar and its reference product are compared using cutting-edge and sensitive techniques capable of detecting relevant structural and functional differences between the products. To address the full range of physicochemical properties or biological activities, multiple independent analytical procedures are used to maximize the possibility that differences between the biosimilar and the reference biologic drug may be detected. Any minor differences in quality observed between the biosimilar and the reference product are assessed in terms of their potential impact on clinical safety and efficacy, and if necessary, additional studies are performed to resolve any areas of residual uncertainty.

Non-Clinical Studies[19,20,29]

Non-clinical studies are conducted to demonstrate that the biosimilar and its reference product have similar pharmacodynamics (PD) and toxicology.

According to the Health Canada guidelines: "Where similarity is well established by structural and functional studies, and where extensive in vitro mechanistic studies are indicative of similarity, in vivo non-clinical studies may not be necessary." In addition, "specialized toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies, are not generally required for a biosimilar submission."[19]

The EMA states, that "These studies include pharmacodynamic studies in vitro, which look at binding and activation (or inhibition) of physiological targets and immediate physiological effects in cells. Pharmacodynamic studies in vivo (animal models) are only done if no suitable in vitro model exists. In vivo toxicological studies are only required in certain cases, for example when the biosimilar is produced in a new type of cell or organism, or when the formulation includes new excipients not used previously."[20]

In contrast, the FDA guideline does not specifically state that the market approval can be granted without in vivo studies.[29]

Clinical Studies[19,29,30]

The aim of the clinical studies is to rule out potential product-related differences that could affect pharmacokinetics (PK), efficacy, or safety, including immunogenicity. The clinical program starts with pharmacokinetic and pharmacodynamic (PD) studies and an assessment of immunogenicity. In most cases, a comparative clinical efficacy trial(s) is(are) important to rule out clinically meaningful differences in efficacy and safety between the biosimilar and the reference product.

Comparative pharmacodynamics studies should use PD-end points that are validated and relevant to clinical outcomes. It is also noted that PD measures (e.g., glucose infusion rate) may be more sensitive in demonstrating clinical similarity than clinical endpoints (e.g., A1C or long-term consequences of diabetes).

For clinical efficacy trials, an equivalence design is generally preferred by the regulators. In some cases, a non-inferiority design may be accepted, if it is clearly justified. The EMA specifies that "adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind" should be done.[30] For clinical efficacy trials, the study end points may be different to those used in the marketing authorization application of the reference product. The end points, however, should be sensitive to detect clinically relevant differences. Also the study population should allow for an assessment of clinically meaningful differences between the proposed biosimilar and the reference product.

Immunogenecity[19,29,31,32]

Health Canada, EMA, and FDA all require studies to show that there are no clinically meaningful differences in immunogenicity between the potential biosimilar and the reference product.

The Health Canada guidelines state that "Of most concern are those antibodies that have the potential to impact safety and/or efficacy; for example, by altering PK, inducing anaphylaxis, or by neutralising the product and/or its endogenous protein counterpart. For each treatment arm, the comparative study(s) should characterize the incidence and magnitude of the anti-drug antibody (ADA) response, the time-course of ADA development, ADA persistence, and the impact of ADA on safety, efficacy and PK."[19]

The EMA has published two guidelines that contain background information on the potential causes and impacts of immunogenicity of biological/biotechnology-derived proteins and provide general recommendations for systematic immunogenicity assessment.[31,32]

The FDA requirements for Immunogenicity Assessment are described in the FDA guidance for industry (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product).[29]

Pharmacovigilance

Health Canada, EMA, TGA, and Medsafe require that companies applying for market authorization submit a tailored risk management plan (RMP) as part of the market authorization submission. In general, the same requirements apply for safety monitoring of biosimilars as for all biologic drugs. The RMP is tailored for each biosimilar product and includes a pharmacovigilance plan and risk minimization measures similar for the reference product or justification why these activities are not relevant for the biosimilar. The RMP should take into account identified and potential risks associated with the reference product and specifically address immunogenicity.[19,20,23,24] Further details regarding the European Union's pharmacovigilance system are detailed in Table 4.

The FDA requires post-marketing safety monitoring.[29] However, it has been noted that the FDA does not have set standards for biosimilars, and a sponsor's approach to post-marketing safety monitoring are developed thorough discussion between the manufacturer and regulator.[33]

Table 4: The European Union — An Example of Pharmacovigilance System for Monitoring, Reporting, Assessing, and Preventing Adverse Drug Reactions[20,34]

In Europe, the risk minimization plan is tailored for each product and it includes a pharmacovigilance plan and risk minimization measures. As for all drugs, companies must collect all reports of suspected adverse drug reactions and submit periodic safety update reports (PSURs). EMA may also require the company to carry out a post-authorization safety study (PASS) that allows monitoring of known risks and also permits detection of rare adverse drug reactions. In some cases, additional pharmacovigilance activities, such as including patients in registries, could be required to monitor long-term or long-latency adverse events.

In addition, all biologic drugs approved after January 1, 2011 are marked with a black triangle that is displayed in the Summary of Product Characteristics (SmPC) and package leaflet with the sentence: "This medicinal product is subject to additional monitoring." The aim of the black triangle is to encourage health care professionals and patients to report any suspected adverse reactions to new drugs.

Interchangeability, substitution, switching

In Canada and US, the term interchangeability refers to a practice of dispensing a drug (generic or biosimilar) instead of reference product at the pharmacy level without consulting the prescriber. The corresponding term used in EU is automatic substitution. The definitions used by different regulators are reported in Table 5.

Table 5: Definitions on Interchangeability, Automatic Substitution, and Switching

Health Canada	**Interchangeability:** Ability for a patient to be changed from one drug to another equivalent drug by a pharmacist, without the intervention of the doctor who wrote the prescription. **Switching:** One-time change from a reference biologic drug to a biosimilar.
FDA	**Interchangeability:** The biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
EMA	**Interchangeability:** The possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by substitution or switching. **Substitution:** Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber. **Switching:** When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.

Source: Health Canada,[1] FDA,[26] EMA and the European Commission.[20]

Health Canada currently does not have any published guidance on interchangeability. In Canada, the policies for interchangeability (at the pharmacy level) are within the remit of each province and territory according to its own rules and regulations. Health Canada recommends that "switching a reference product to a biosimilar should be made by the treating physician in consultation with the patient and taking into account available evidence and any policies of the relevant jurisdiction."[1]

In the US, interchangeability has been defined in legislation (BPCI Act) and the FDA has published a draft guidance on considerations in demonstrating interchangeability with a reference product.[26] In general, a biosimilar may be interchangeable with a reference product if it meets additional standards for interchangeability. The manufacturer has to prove that an interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient" and that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[25] According to BPCI Act, biosimilars designated by the FDA as interchangeable may be substituted for the reference product without the intervention of the prescriber. However, the laws regarding drug substitution fall within the remit of individual states.[35,36]

To demonstrate interchangeability to the FDA, a sponsor would generally have to provide data from a switching study or studies that assess PK measures, clinically relevant and sensitive PD measures, immunogenicity, and safety in a population that is adequately sensitive to the possible effects of switching. The general requirements of study end points, study design and analysis, study population, and conditions of use to be studied, as well as route of administration are outlined in the draft guidance. However, the FDA approach to any necessary switching studies is flexible and it encourages sponsors to have early discussions with the FDA about their product development plans.[26]

In the EU, the EMA does not provide guidance on interchangeability, substitution, or switching. These policies are within the remit of member countries.[20] Several national authorities in Europe have published positions supporting physician-led switching.[37,38] It should be noted, however, that the national position papers do not generally support interchangeability at the pharmacy level without consulting the prescriber.

Authorization of Indications

Health Canada, the EMA, and the FDA can authorize biosimilars for indications where clinical studies were not conducted as long as it is supported by sufficient scientific justification and as long as all the submitted evidence — including quality, non-clinical, and clinical studies — have been found satisfactory. The term extrapolation is often used by international regulators to describe this process. Extrapolation has been defined as the "extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication approved for the reference medicine."[20] Table 6 describes the factors that may be considered by Health Canada, the FDA, and the EMA when indications are authorized without a clinical study.

Table 6: Regulatory Considerations Related to the Authorization of Indications in Canada, the US, and the EU

Health Canada	The decision to authorize the requested indications is dependent on the demonstration of similarity between the biosimilar and reference biologic drug based on data derived from comparative structural, functional, non-clinical, and clinical studies. A detailed rationale that scientifically justifies authorization of the biosimilar in each indication should be provided taking into consideration: • mechanism(s) of action • pathophysiological mechanism(s) of the disease(s) or conditions involved • safety profile • dosage regimen • clinical experience with the reference biologic drug • case-by-case considerations. Certain situations may warrant additional clinical data for a particular indication.[19]
FDA	"Scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use: • The mechanism of action in each condition of use for which licensure is sought; this may include: ◦ The target/receptor(s) for each relevant activity/function of the product ◦ The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s) ◦ The relationships between product structure and target/receptor interactions ◦ The location and expression of the target/receptor(s) • The PK and bio-distribution of the product in different patient populations (Relevant PD measures may also provide important information on the mechanism of action). • The immunogenicity of the product in different patient populations • Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to off-target activities) • Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the *totality of the evidence* supporting a demonstration of biosimilarity."[29]

EMA	Extrapolation should be considered in the light of the totality of data, i.e., quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physicochemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as: • the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications • the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications • the studied therapeutic indication is not relevant for the others in terms of efficacy or safety; i.e., is not sensitive for differences in all relevant aspects of efficacy and safety. Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g., co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.[30]

In addition to the benefit/risk-based considerations of market authorization, there is the issue of patents. The manufacturer of the originator biologic drug holds various patents based on indications. Manufacturers of biosimilars seeking approval for multiple indications can only be granted market authorization once patents have expired. As patents would have been granted at different times for each of the indications and for the different jurisdictions, the timing of the availability of a biosimilar may differ by indication and across jurisdictions. The manufacturer may also choose to apply for market authorization of a biosimilar for the various indications at different times within each jurisdictions.[1]

Naming and Labelling

Currently, there is no international harmonization on the naming of biosimilar products. The World Health Organization (WHO) has proposed to add a four-letter code ("biological qualifier") to the international non-proprietary names (INNs).[39] EMA accepts the use of the same INNs for biosimilars as it does for reference products (e.g., infliximab), with products distinguished by brand name and batch number. FDA uses a random four-letter suffix (e.g., infliximab-dyyb and infliximab-abda).[40] Health Canada is currently evaluating the most appropriate naming convention for biologic drugs; in the meantime, reference products and biosimilars are identified by unique brand name and shared non-proprietary name.

Health Canada released a new product monograph template for biosimilars in May 2017.[41] In Canada, the product monograph for a biosimilar should include a statement indicating that the product is a biosimilar, and that the indications have been granted on the basis of similarity between the biosimilar and the reference product. The biosimilar product monograph should also summarize the comparative data on which the decision for market authorization was based, in tabular format. In addition, relevant safety and efficacy information from the product monograph of the reference product should be included. A detailed description of labelling requirements is provided in the Health Canada Guidance document and product monograph template.[19,41]

In the US, product labelling should state that the product is a biosimilar to a reference product. The labelling should incorporate relevant data and information from the labelling of the reference product, but modifications specific to the biosimilar product are allowed. The FDA does not generally recommend inclusion of the comparative data that demonstrated biosimilarity in product labelling. A detailed description of the FDA's labelling recommendations is provided in their draft guidance.[18]

In the EU, an SmPC forms the basis of product information for health care professionals. In the SmPC, the product is identified as a biosimilar. Biosimilar SmPCs also contain a black triangle that indicates that the product is subjected to additional post-authorization monitoring by EMA. Otherwise, the SmPC of a biosimilar is aligned with the SmPC of the reference product. The biosimilar's SmPC mentions the name of the active substance (i.e., the INN) and not the brand name of the reference product. The details of comparability studies that demonstrated biosimilarity are reported in the European Public Assessment Report (EPAR).[20]

In Australia, the product information is expected to include a statement that the product is a biosimilar product to a reference product.[24] The guidance also states that:

- "any clinical trial information generated on the reference medicine that is reported in the reference medicine product information and included in the biosimilar product information is clearly identified as having been produced using the reference medicine and not the biosimilar."
- "comparative clinical trial information between the biosimilar medicine and the reference medicine should be clearly identified in the CLINICAL TRIALS and ADVERSE EFFECTS sections."

HTA Process for Biosimilar Reviews

Based on the responses from the HTA organizations that were consulted for this Environmental Scan, four different approaches for reviewing biosimilars were identified:

- **The review process follows the same process as that for new drugs:** The clinical and economic review processes for biosimilars are the same as the regular review process that is followed for new drugs in the context of a single technology assessment.
- **Tailored approach:** Biosimilars undergo a tailored clinical and/or economic review process.
- **Review process is dependent on the status of the reference product:** Biosimilars are reviewed only if their reference product is not appraised or has been appraised but it is not reimbursed.
- **Biosimilars are not routinely reviewed:** Biosimilars are not generally reviewed by the HTA organization unless specifically requested by the decision-maker(s).

The responses for the email survey were received up to August 8, 2017 and describe the processes that were in place at the time of writing this report. The approach used by each HTA organization that was consulted is indicated in Table 7.

Table 7: Approaches Used for Reviewing Biosimilars in Selected HTA Organizations

	Review Follows the Same Process as for New Drugs	Tailored Review Process	Review Depends on the Status of the Reference Product	Not Routinely Reviewed
Canada / CADTH		x		
Canada / INESSS	x			
Australia / PBAC	x[a]	x[a]		
New Zealand / PHARMAC	x			
Finland / Hila		x		
Finland / Fimea				x
France / HAS	x			
Germany / IQWiG				x
Netherlands / ZIN				x
Norway / NoMa			x	
UK / NICE		x		
UK / SMC			x	

[a] Biosimilar submissions can be either major or minor, depending on the issues that need to be addressed.

Canada

In Canada, there are two HTA agencies that provide reimbursement recommendations to participating public drug plans and cancer agencies — CADTH and the Institut national d'excellence en santé et en services sociaux (INESSS) — both of which review biosimilars. INESSS is responsible for providing drug reimbursement recommendations specifically for the province of Quebec.

Non-oncology biosimilars are reviewed by CADTH's Common Drug Review (CDR) and biosimilars for oncology indications are reviewed by CADTH's pan-Canadian Oncology Drug Review (pCODR). CDR and pCODR reviews are generally based on submissions from a manufacturer; however, public drug plans, cancer agencies, and tumour groups may also make a request for a drug to be reviewed. At CADTH, the applications for biosimilars undergo a tailored review and have specific submission requirements.[42,43] A summary of CADTH reimbursement recommendations for biosimilars up to August 21, 2017 is provided in Appendix C. On August 1, 2017, CADTH invited stakeholder comments and feedback for proposed revisions to the process for reviewing biosimilars submitted through CADTH's CDR and pCODR programs. The aim of the proposed revisions is to take a more streamlined approach to biosimilar reviews in order to avoid duplication of work, optimize resources, and ensure that all participating drug plans and cancer agencies continue to benefit from a national approach to evidence reviews.

INESSS evaluates the registration applications for biosimilars using the same process as for brand name drugs with a drug identification number (DIN) assigned by Health Canada. Therefore, the manufacturer is required to submit a complete application to INESSS.[44,45] INESSS has not published a position statement on interchangeability, switching, or substitution.

Australia

In Australia, PBAC makes recommendations on the listing of new medicines on the Pharmaceutical Benefits Scheme. Biosimilar submissions can be either major or minor, depending on the issues that need to be addressed.

Major submissions typically relate to listing requests for new drugs or new therapeutic indications for currently listed drugs. In a major submission, an economic model is required to support a claim of cost-effectiveness, cost-utility, or cost-minimization. Minor submissions can relate to listing of a new form or strength of an already-listed drug that has a bioequivalence or equivalence statement from the regulator (TGA). In minor submissions, an economic model is not necessary. Biosimilar submissions to PBAC may be either minor or major depending on the issues that need to be addressed for the particular review. Minor submissions may be "appropriate for a new biosimilar brand of an existing pharmaceutical item with no indication changes."[46] If a submission is made to PBAC and is considered by the Department of Health to be misclassified, the Department of Health will review and reclassify the submission. Sponsors who are uncertain of the type of submission required are requested to contact the Government of Australia's Department of Health with a request for further information.

PBAC supports the substitution of a biosimilar and its reference product at a pharmacy level. The substitution status is assessed on a case-by-case basis taking into account the evidence presented in each submission to list a biosimilar drug.[47,48]

New Zealand

In New Zealand, PHARMAC is responsible for managing the funding of pharmaceuticals on behalf of the district health boards. PHARMAC reviews biosimilars using their regular funding application process. Therefore, PHARMAC's review process for biosimilars is the same as the regular review process that is followed for new drugs in the context of a single technology assessment.[49]

PHARMAC considers that biosimilars offer considerable potential to increase competition, reduce costs, and improve access for patients in New Zealand. PHARMAC has not published a position statement on the interchangeability, substitution, or switching of biosimilars.

Europe

Biosimilars in the member states of the EU and the European Economic Area (EEA) are granted market approval through a centralized process. However, conducting HTAs (including evidence review and reimbursement recommendations or decision-making) is the responsibility of individual member states. For that reason, there are multiple national and regional HTA organizations that review pharmaceuticals in Europe. The approaches that different organizations follow vary because of the differences in their health care systems.[50]

The HTA processes for biosimilars in selected European countries are described below. In addition, there is a demand for enhanced cooperation of HTA in Europe. The current EU-level cooperation consists of a strategic (HTA Network) and scientific and technical level (EUnetHTA Joint Action 3) activities. EUnetHTA does not have a position paper or any HTA processes related specifically to biosimilars. (Ingvil Saeterdal, EHnetHTA/Norwegian Institute of Public Health NIPHNO, Oslo: personal communication, 2017 Jun.)

Finland

The reimbursement of biosimilars and all other drugs dispensed from community pharmacies in Finland is possible only after the Pharmaceuticals Pricing Board has approved the reimbursement status and a reasonable wholesale price for the product. If a drug contains a new active pharmaceutical ingredient or the indication for the reimbursement status is going to be significantly expanded, the pharmaceutical company must include a health economic evaluation in their application to the Pharmaceuticals Pricing Board. Since a biosimilar is not considered a new active substance, a health economic evaluation is not included in the biosimilar applications. The Pharmaceuticals Pricing Board does not have a position statement on biosimilars.

In Finland, market authorization holders do not typically apply for reimbursement for drugs administered in the hospital setting because there is a two-channel financing and dispensing system. Therefore, the Pharmaceuticals Pricing Board does not generally make reimbursement decisions on drugs that are administered in the hospital setting (e.g., infusions). The Finnish Medicines Agency (Fimea) produces HTA reports on new drugs that are administered in hospitals.[51] Fimea has not produced HTA reports on biosimilars and does not have a dedicated HTA process regarding biosimilar drugs. As the national competent authority for regulating pharmaceuticals in Finland, Fimea has published a position statement supporting the interchangeability of biosimilars with their reference products under the supervision of a health care professional.[52] It should be noted, however, that Fimea's position does not support the substitution of the reference product for a biosimilar at the pharmacy level.

France

In France, HAS is in charge of the HTA process for all drugs including biosimilars. Currently, the review process for biosimilars is the same as the regular review process that is followed for all drugs.[53] Discussions are under way, however, for a fast-track process for the review of biosimilars. If approved, the process would be the same as what exists for generic drugs in that biosimilars would no longer be reviewed by HAS. Biosimilar applications would be

directly transmitted to the economic committee for price negotiation provided that HAS had previously issued an opinion on the reference product. If the biosimilar review process was to be changed in France, a revision to the legislation would be needed.

HAS does not have a published position statement on interchangeability, switching, or substitution of biosimilars. The position of HAS, however, is in line with French legislation (Social Security Financing Act for 2014 [LFSS 2014] for substitution and Social Security Financing Act for 2017 [LFSS 2017] for interchangeability [article 96]). In France, the legislation stipulates that substitution of the first prescription of a biologic drug at the pharmacy level is allowed. But a prescriber may exclude substitution by the words "non-substitutable" on the prescription. However, the substitution of biosimilars is not currently in effect because, among other things, there is lack of a reference list for biologics/biosimilars (substitutable drugs should belong to the same similar biological group) and a lack of a national pharmaceutical database for prescriptions.

The decree n° 2016-960 of July 12, 2016 stipulates the process of elaboration of the reference list for biologics/biosimilars. This decree was published after LFSS 2014. The decree indicates that the list of similar biological groups should be presented by reference biologic drug. The name, dosage, pharmaceutical form, common name of the active substance, name of the marketing authorization holder, its therapeutic indication(s) and, where appropriate, the excipients with known effects should be indicated. The decisions to register a medicinal product on the reference list of similar biological groups, to amend such decisions, and to remove them from the list are taken by the Director General of ANSM (L'Agence nationale de sécurité du médicament et des produits de santé) and published on the Agency's website. No similar biological group have yet been published on ANSM's website.

In France switching is allowed and is under the physician's responsibility and should respect three conditions:

- a patient being treated with a biologic drug must be informed of, and agree to switching
- the patient must receive appropriate clinical monitoring during treatment
- traceability of the products concerned must be ensured.[54]

Germany

The responsibilities of IQWiG include the assessment of the benefits and costs of drugs. IQWiG, however, does not review biosimilars, unless specially requested by the Federal joint Committee (G-BA). To date, no requests have been made. If IQWiG would review a biosimilar product, the process would follow the general procedures used by the institute.[55] IQWiG has not published a position paper on interchangeability, switching, or interchangeability of biosimilars.

Netherlands

The National Health Care Institute's (Zorginstituut Nederland, ZIN) duties include managing the basic health care package in order to ensure that it contains all necessary care. This responsibility includes reviewing pharmaceuticals. However, ZIN does not review biosimilars unless there is a legal dispute between an insurer and payer. This has not happened in the past. In addition, ZIN does not have a position statement on biosimilars.

Norway

NoMa is responsible for reviewing new drugs including biosimilars, in Norway. NoMa does not review biosimilars if the reference product has already been reviewed (through their HTA process) and is used in public health care. In that case, the biosimilar will be reimbursed at the same price and for the same indications that are approved for the reference products. If the reference product is not reimbursed or publicly financed, the biosimilar review process follows the regular single technology assessment (STA) process for pharmaceuticals.[56,57]

NoMa has not yet published a position statement on interchangeability, switching or substitution of biosimilars, but the writing of such a document is in process. NoMa has recommended a legislative amendment to enable substitution of biologics/biosimilars at the pharmacy level without consulting the prescriber. If the law is changed, NoMa will assess the substitutability of each drug on a case-by-case basis, as they do for generic drugs, to be sure that automatic substitution at the pharmacy level is safe.

United Kingdom

The SMC's current policy states that biosimilars are not reviewed if the reference product has been accepted by SMC/Healthcare Improvement Scotland (HIS) for the same indication(s) and in the same population or if the reference product was initially licensed and available before January 31, 2002.[58] For that reason, SMC will not routinely assess biosimilar drugs on the basis of a full submission. Health boards are expected to make local formulary decisions on the use of these products.

However, if the reference product is not recommended by SMC/HIS, a full submission will be required.[59] Also in situations where a biosimilar is anticipated to have an impact on the National Health Service (NHS) Scotland resources, SMC reserves the right to request a full submission.

HIS (the wider organization that SMC belongs to) in collaboration with NHS boards and Area Drug and Therapeutics Committees has produced a national prescribing framework for biosimilars. The framework advises that "individual patients may be switched to another biologic drug, including a biosimilar drug, as part of a clinician-led management programme which has appropriate monitoring in place."[60]

NICE will consider reviewing any biosimilar that is brought forward by the National Institute for Health Research Horizon Scanning Centre. If reviewed, biosimilars will usually be part of a Multiple Technology Appraisal (MTA) alongside their reference products.[61] The Single Technology Appraisal (STA) process, that is typically used to provide recommendations on the use of new drugs in the NHS, is not used for biosimilars. The process and scope of MTA differs from that of STA. In MTA, for example, the relevant evidence is gathered from several sources. In the STA process, clinical, and economic evidence, mainly provided by the market authorization holder, is reviewed. In the STA process, a single product for a single indication is appraised. In MTA single or multiple products with one or more related indications are appraised.[62]

When it is considered that a review of the evidence for the biosimilar is necessary, NICE will consider producing an "Evidence summary new medicine" on biosimilars.[61] Evidence summaries do not include recommendations. For that reason, the choice between the biosimilar and the reference product for an individual patient is made by the responsible clinician in consultation with the patient.

In the UK, it is recommended that "all biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient."[63]

Reimbursement Frameworks for Biosimilars

Canada

In Canada, the federal, provincial, territorial public drug plans and cancer agencies determine the reimbursement criteria for drugs, including individual biosimilars, based on the recommendations issued by CADTH and INESSS. The reimbursement criteria are based on recommendations issued by CADTH's expert committee called the Canadian Drug Expert Committee (CDEC) for CDR non-cancer indications or by pCODR's Expert Review Committee (pERC) for cancer indications.[64,65] The joint federal, provincial, territorial price negotiations are conducted by the pan-Canadian Pharmaceutical Alliance (pCPA).[66]

In April 2016, pCPA issued the First Principles for Subsequent Entry Biologics (SEBs) to guide their approach to negotiations on biosimilars and reference biologics.[67] According to the principles:

- All biosimilar and reference biologic manufacturer proposals will only be considered through the national pCPA negotiation process rather than individual or selected jurisdictions.
- Products under consideration by the pCPA will be informed by Health Canada's regulatory determinations, HTA recommendations, and/or other evidence or considerations as available.
- To increase patient access to clinically and cost-effective drug treatment options, the pCPA will encourage a competitive environment that includes biosimilar market growth and is conducive to long-term cost reductions and sustainability for public drug plans.
- The introduction of a biosimilar must provide a reduction in the drug's transparent price to benefit all Canadians.
- Proposals from reference biologic manufacturers will be considered only if they:
  - Provide overall national value to public drug plans and do not result in incremental costs to individual jurisdictions; and
  - Provide at least similar overall value compared with the biosimilars, and must include similar or better transparent price reductions if equivalent listing status is sought.

As of October 31, 2017, pCPA has completed negotiations on Inflectra (infliximab), Grastofil (filgrastim), Basaglar (insulin glargine), Brenzys (etanercept), and Erelzi (etanercept).[68]

An overview of the current state of biosimilars in Canada, including provincial funding statuses for Omnitrope and Inflectra, is provided in an article by Siu et al.[69] All provinces provide funding for Omnitrope. However, there is variability in the indications that are reimbursed (e.g., in Ontario, all Health Canada–approved indications are reimbursed, and in Quebec, reimbursement is for children only). Table 8 provides a summary of the drug program funding status for infliximab and etanercept originator and biosimilar products. In most provinces infliximab-naive patients are required to start their treatment on Inflectra (biosimilar), but patients stable on Remicade (reference product) do not have to switch to Inflectra. In Quebec, patients are required to use the infliximab product that has the lowest price or pay the difference in price (except if "no substitution" is requested by the prescriber).

Table 8: Federal and Provincial Drug Programs Funding Summary for Etanercept and Infliximab

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[81]
Enbrel (etanercept)													
rheumatoid arthritis	RES (for patients granted SA prior to July 18, 2017)	RES	RES	RES	RES	RES	RES	RES	RES	RES (patients grand-fathered)	RES	RES	RES
ankylosing spondylitis		RES	RES	RES	RES	RES	RES	RES	RES		RES	RES	RES
polyarticular juvenile idiopathic arthritis	RES	RES	RES	not a benefit	RES	RES	RES	RES	RES	not a benefit	RES	not a benefit	not a benefit
psoriatic arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
plaque psoriasis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	not a benefit	RES	RES
pediatric plaque psoriasis	not a benefit	RES	not a benefit	RES	not a benefit	RES	RES	not a benefit	not a benefit	not a benefit	not a benefit	not a benefit	not a benefit
Brenzys (etanercept-biosimilar)													
rheumatoid arthritis	RES	RES	UR	RES	LU	UR	UR	RES	RES (effective date of Sept. 25, 2017)	RES (all new patients)	UR	UR	not a benefit
ankylosing spondylitis	RES	RES	UR	RES	LU	UR	UR	RES	RES (effective date of Sept. 25, 2017)		UR	UR	not a benefit
Erelzi (etanercept-biosimilar)													
rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis	Negotiation with pCPA complete as of October 31, 2017[68]												

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[81]
Remicade (Infliximab)													
rheumatoid arthritis	RES (for patients granted SA prior to Feb. 19, 2016)	RES (for patients granted SA prior to April 1, 2016)	RES	RES	RES (for patients granted EAP approval prior to Feb. 26, 2016)	RES (for patients granted EDS prior to June 1, 2016)	RES (to patients granted SA prior to June 1, 2016)	RES (for patients granted SA prior to June 1, 2016)	not a benefit	RES (patients grand-fathered)	RES (for patients approved prior to May 1, 2017)	RES	RES
ankylosing spondylitis			RES	RES					not a benefit		not a benefit	RES	RES
psoriatic arthritis			RES	RES		RES (for patients granted EDS prior to Dec. 1, 2016)	RES (to patients granted SA prior to June 1, 2016)		not a benefit		not a benefit	UR	RES
plaque psoriasis			RES	RES		RES (for patients granted EDS prior to June 1, 2016)	RES (to patients granted SA prior to June 1, 2016)		not a benefit		not a benefit	RES	RES
Crohn's disease	RES (for patients granted SA prior to Nov. 1, 2016)	RES (for patients granted SA prior to Dec. 1, 2016)	RES	RES	RES (for patients granted EAP approval prior to Nov. 30, 2016)	RES (for patients granted EDS prior to Dec. 1, 2016)	RES (to patients granted SA prior to Nov. 30 2016)	RES (to grand-fathered patients)	not a benefit		RES (for patients approved prior to May 1, 2017)	RES	RES
fistulizing Crohn's disease			RES	RES		RES (for patients granted EDS prior to Dec. 1, 2016)	RES (to patients granted SA prior to Nov. 30 2016)	RES (to grand-fathered patients)	not a benefit		RES (for patients approved prior to May 1, 2017)	RES	RES

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[81]
ulcerative colitis	not a benefit		RES	RES	RES (for patients granted EAP approval prior to Nov. 30, 2016)	RES (for patients granted EDS prior to Dec. 1, 2016)	not a benefit	not a benefit	not a benefit		not a benefit	UR	RES
pediatric Crohn's disease	EC	not a benefit	RES	RES	not a benefit	RES	RES	case by case	not a benefit	not a benefit	RES	not a benefit	not a benefit
pediatric ulcerative colitis	EC	not a benefit	RES	RES	not a benefit	RES	not a benefit	case by case	not a benefit	not a benefit	not a benefit	not a benefit	not a benefit
Inflectra (infliximab-biosimilar)													
rheumatoid arthritis	RES	RES (for new patients)	RES	RES	LU	RES (for new patients)	RES (all patients)	RES (new patients)	RES	RES (all new patients)	RES	RES (new patients)	not a benefit
ankylosing spondylitis			RES	RES	LU				RES		RES		not a benefit
psoriatic arthritis			RES	RES	LU				RES		RES	UR	not a benefit
plaque psoriasis			RES	RES	LU				RES		RES	RES (new patients)	not a benefit
Crohn's disease			RES	RES	LU				RES		RES	UR	not a benefit
fistulizing Crohn's disease			RES	RES	LU	RES (for new patients)	RES (all patients)		RES		RES	UR	not a benefit
ulcerative colitis			RES	RES	LU	RES (for new patients	RES (all patients)	RES (all patients)	not a benefit		RES	UR	not a benefit

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[81]
Remsima (infliximab-biosimilar)													
rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, fistulizing Crohn's disease, ulcerative colitis	Listed with "Dormant status" in the Health Canada Drug Product Database.[86] Dormant status "refers to an active DIN that was previously marketed in Canada but for which the manufacturer has suspended sale for period of at least 12 months"[87]												

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; EAP = Exceptional Access Program; EC = exceptional coverage; EDS = exceptional drug status; LU = limited use benefit; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits plans; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; pCPA = pan-Canadian Pharmaceutical Alliance; PEI = Prince Edward Island; RES = restricted benefit with specified criteria (includes special authorization, exception drug status, etc.); SA = special authorization; SK = Saskatchewan; UR = under review; VAC = Veterans Affairs Canada; YK = Yukon.

Australia

In Australia, PBAC considers marking biosimilars as equivalent with its reference product ("a" flagging) on a case-by-case basis.[47] If a biosimilar is "a" flagged, it is suitable for substitution at the pharmacy level. PBAC has advised that the following considerations would be relevant when assessing if the biosimilar product is suitable for "a" flagging:[48]

- absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator product
- absence of identified populations where the risks of using the biosimilar product are disproportionately high
- availability of data to support switching between the originator product and the biosimilar product
- availability of data for treatment-naive patients initiating on the biosimilar product
- whether the Therapeutic Goods Administration has deemed a product to be biosimilar with the originator product.

Brenzys (etanercept) is the first biosimilar available through community pharmacies in Australia. Brenzys and its reference product (Enbrel) are "a" flagged and thus can substituted at the pharmacy level without consulting the prescriber. However, the pharmacist cannot dispense a brand other than the one that was prescribed if a doctor has ticked the "brand substitution not permitted" box when writing a prescription.[88]

New Zealand

PHARMAC invites tenders for the supply of biosimilars to District Health Board (DHB) hospitals and/or to community pharmacies in New Zealand. The first biosimilar funded in New Zealand was Zarzio (filgrastim) and it was awarded a Sole Subsidised Supply Status.[89] Also Remicade has been awarded a sole supply status and it is now the only funded brand of infliximab for all currently funded indications to be used in DHB hospitals.[90]

Europe

Different European countries apply different reimbursement strategies for biosimilars, including mandatory price-cuts, prescription incentives, or quotas and substitution regulations. A recent report from Simon-Kurcher et al. provides an overview of current biosimilar medicines pricing and market access policies used in France, Germany, Italy, Spain, the UK, Norway, and Poland.[8] This report summarizes the policies into four domains: general price and market access regulations, drug procurement, drug prescription, and drug dispensation. In Table 9, the biosimilar pricing policies are described.

In a similar manner, a review form Renwick et al. described post market policies for biosimilar oncology drugs in Belgium, France, Germany, Italy, Netherlands, Norway, the UK, and the US.[7] The policies were characterized in six domains: interchangeability, physician prescribing, substitutability, pharmacist dispensing, hospital financing, and tendering and pricing.

Based on the two reviews, different countries use different sets of strategies for biosimilar pricing and reimbursement. It is not possible to identify a single best biosimilar policy. For example, the high biosimilar uptake in Norway is a result of a unique combination of drivers, including national single-lot, multi-winner tender, gainsharing at the hospital level, and high physician acceptance of biosimilars.[8]

An upcoming report from PMPRB will also provide information on international pricing and reimbursement policies.[91]

Table 9: Examples of Pricing Policies for Biosimilars and Their Reference Products[8]

Country	
France	**Hospital setting** • Reference product: at least –10% • Biosimilar: equal to or lower than the price of reference product **Retail setting** • Reference product: –15% to –20% • Biosimilar: –25% to –35% relative to reference product's initial price
Finland[92]	**Hospital setting:** • Biosimilar: Free pricing (however, discount relative to reference product expected) **Retail setting:** • first biosimilar drug entering the reimbursement system has to be 30% less than the price of the reference product
Germany	• Biosimilar: Free pricing (however, major discount relative to reference product expected) • Reference product: No specific rules/regulations; however, if a FRP group is created, the originator's list price will usually be adjusted to the FRP level to be fully reimbursed
Italy	• Biosimilars: at least –20% than the price of reference product • Reference product: No mandatory discount after loss of exclusivity (however, Italian Medicines Agency [AIFA] have started renegotiating prices of reference products where reimbursement has not yet been filed for biosimilar medicines)
Spain	• Reference product: No mandatory discounts after loss of exclusivity / biosimilar entry beyond (mandatory) creation of FRP group • FRP group: For reference product and biosimilar, after the loss of exclusivity / biosimilar entry (however, given the purchasing system in place for hospital drugs, the FRP price is not very relevant). Expected discounts for originator and biosimilar: –25% to –30%.
UK	Reference product: No defined pricing rules after launch of biosimilar medicines Biosimilar: Free pricing for biosimilar medicines — included under and indirectly controlled by Pharmaceutical price Regulation Scheme
Norway	Biosimilars: 9% mandatory discount required vs. reference product list price in order to be listed by the Norwegian Drug Procurement operation

FRP = fixed reference price.

Canadian Market Information

The 30 top selling biologic drugs in Canada are listed in Appendix D. The sales of these 30 biologics accounted for 24% of the pharmaceuticals sales in Canada in 2016.

Many of the top selling biologic drugs already have or are expected to have biosimilars with the next few years. PMPRB has identified 13 reference products that have recently launched biosimilars or biosimilars that are expected to be launched over the next three years in Canada (Table 10).[3] The sales of these 13 branded products summed up to $3.6 billion in 2016. In addition to the 13 products, a biosimilar for Humalog (insulin lispro) is already authorized and the biosimilar for Neulasta (pegfilgrastim) is under review in the EU.

Table 10: Biologic Drugs (reference products) With Recently Launched Biosimilars or With Biosimilars That Are Expected to Be Launched Within the Next Three Years in Canada[3]

Active Substance	Brand Name	First NOC[16]	2016 Sales (C$)[a]
Infliximab	Remicade	2001	1,004M
Adalimumab	Humira	2004	649M
Ranibizumab	Lucentis	2007	337M
Etanercept	Enbrel	2000	337M
Rituximab	Rituxan	2000	241M
Insulin glargine	Lantus	2002	241M
Trastuzumab	Herceptin	1999	180M
Filgrastim	Neupogen	1996[b]	126M
Omalizumab	Xolair	2004	106M
Bevacizumab	Avastin	2005	104M
Epoetin alfa	Eprex	1995[b]	99M
Natalizumab	Tysabri	2006	50M
Follitropin alfa	Gonal-F	1997	14M

NOC = notice of compliance.

[a] For the brand name product.

[b] Source: QuintilesIMS MIDASTM Database 2016.

The percentage price difference between biosimilars and their reference products are not as great as the price differences between generics and brand drugs. Nevertheless, the potential for cost saving is substantial given the high cost of biologic drugs. In Canada, the biosimilar price reductions are reported to range from 12% to 23% relative to the reference product.[3] The exception is infliximab, that has a biosimilar discount of nearly half (47%) of the price of the reference product.[69] In Canada, however, the prices of reference product are markedly higher than prices in the majority of other OECD countries.[3]

In Europe, biosimilars have been priced 6% to 37% lower, on average, than their reference products the year before biosimilar entry, but price reductions as high as 66% have been reported.[6] The extent by which biosimilar competition has an impact on price, however, appears to vary considerably between biosimilar drugs, therapeutic areas, and European countries. It is also important to note that increased biosimilar competition in Europe has not only affected the prices of the directly comparable biosimilars and their reference product but

also the whole product class. The European experience shows that savings can be achieved through price regulation interventions and/or commercial decisions of manufacturers even if the market share of biosimilars is low.

Reimbursement recommendations for the reference products

CADTH reimbursement recommendations for the 13 reference products identified by PMPRB for all Health Canada–approved indications are listed in Table 11. A more detailed description of the CDEC or pERC recommendations is provided in Appendix E. The majority of the reviewed products have been recommended to be listed with clinical criteria or conditions.

Table 11: CADTH Reimbursement Recommendations for Reference Products

Active Substance	Brand name	Indications	CDEC or pERC recommendation
Infliximab	**Remicade**	Rheumatoid arthritis	—[a]
		Ankylosing spondylitis	—
		Adult Crohn's disease	—
		Pediatric Crohn's Disease	—
		Fistulizing Crohn's disease	—
		Pediatric ulcerative colitis	—
		Psoriatic arthritis	—
		Plaque psoriasis	—
		Ulcerative colitis	DNL
Adalimumab	**Humira**	Rheumatoid arthritis	LWCC
		Polyarticular juvenile Idiopathic arthritis	LWCC
		Psoriatic arthritis	LWCC
		Ankylosing spondylitis	LWCC
		Adult Crohn's disease	LWCC
		Pediatric Crohn's disease	—
		Ulcerative colitis	DNL at submitted price
		Hidradenitis suppurativa	LWCC
		Plaque psoriasis	LWCC
		Uveitis	—
Ranibizumab	**Lucentis**	Macular degeneration, age-related	LWCC
		Macular edema, diabetic	LWCC
		Macular edema, secondary to retinal vein occlusion	LWCC
		Choroidal neovascularization, myopic	LWCC
Etanercept	**Enbrel**	Rheumatoid arthritis	—
		Juvenile Idiopathic arthritis	—
		Psoriatic arthritis	—
		Ankylosing spondylitis	—
		Plaque psoriasis	—
		Pediatric Plaque psoriasis	—

Active Substance	Brand name	Indications	CDEC or pERC recommendation
Rituximab	**Rituxan**	Rheumatoid arthritis	LWCC
		GPA or MPA	LWCC
		Non-Hodgkin's lymphoma	—
		Chronic lymphocytic leukemia	—
		Hodgkin's lymphoma	—
		Indolent Non-Hodgkin's lymphoma and mantle cell Lymphoma	RWCC
		BMT	—
Trastuzumab	**Herceptin**	Early breast cancer	—
		Metastatic breast cancer	RWCC[b,c]
		Metastatic gastric cancer	—
Insulin glargine	**Lantus**	Diabetes mellitus, Type 1 & 2	DNL
Filgrastim	**Neupogen**	Neutropenia	—
Pegfilgrastim	**Neulasta**	Neutropenia	LWCC
Omalizumab	**Xolair**	Asthma, severe persistent	DNL
		Urticaria, chronic idiopathic	LWCC
Bevacizumab	**Avastin**	Metastatic colorectal cancer	RWCC[d, e,]
		Non–Small cell lung cancer	—
		Cervical cancer	RWCC
		Ovarian cancer	RWCC
		Platinum-sensitive ovarian cancer	—
		Platinum-resistant ovarian cancer	RWCC
		Recurrent glioblastoma	—
Epoetin alfa	**Eprex**	Anemia in several indications	—
Natalizumab	**Tysabri**	Multiple Sclerosis, relapsing-remitting	LWCC
Follitropin alfa	**Gonal-F**	Stimulation of follicular development	—

DNL = do not list, GPA = granulomatosis with polyangiitis; LWCC = list with clinical criteria/conditions; MPA = microscopic polyangiitis, RWCC = reimburse with conditions/criteria.

[a] Not reviewed by CADTH, as NOC received before the inception of CDEC.

[b] In combination with pertuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

[c] For the treatment of patients with metastatic breast cancer whose tumours overexpress HER2.

[d] Only reviewed in combination with capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (CRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy.

[e] In combination with fluoropyrimidine-based chemotherapy for first-line treatment of patients with metastatic colorectal cancer.

Provincial funding for the reference products

The public payers in Canada have taken different approaches for funding the 13 reference products. Table 12 outlines the provincial funding statuses for oncology products. The federal, territorial, and provincial drug program funding statuses for selected non-oncology products are reported in Appendix F.

Table 12: Provincial Funding Summary for Oncology Reference Products (as of July 12, 2017)[93-97]

	BC	AB	SK	MB	ON	NS	NB	NL	PEI
Bevacizumab (Avastin)									
Metastatic Colorectal Cancer (mCRC): in combination with fluoropyrimidine-based chemotherapy for first-line treatment of patients with mCRC.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non–small cell lung cancer (NSCLC): in combination with carboplatin/paclitaxel chemotherapy regimen for treatment of patients with unresectable advanced, metastatic or recurrent non-squamous NSCLC.	×	×	×	✧	×	×	×	×	×
Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer: in combination with carboplatin and gemcitabine for the treatment of patients with first recurrence platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. These patients should not have received prior VEGF-targeted therapy including AVASTIN.	×	×	×	×	×	×	×	✧	×
Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer: with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. These patients should not have received prior VEGF-targeted therapy including AVASTIN.	†	†	†	†	†	†	†	†/✧	†
NOC/c Malignant Glioma (WHO Grade IV) — Glioblastoma: as a single drug for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.	✓	×	✓	✓	×	×	×	✓	×
Metastatic Colorectal Cancer (mCRC): in combination with capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (CRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy.	†	†	†	†	†	†	†	†	†

	BC	AB	SK	MB	ON	NS	NB	NL	PEI
Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients.	†	✓	✓	✓	✓	✓	✓	✓	†
Cervical Cancer: in combination with chemotherapy for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix.	✓	✓	✓	✓	✓	✓	✓	✓	†
Malignant Pleural Mesothelioma: In combination with pemetrexed and cisplatin or carboplatin (for cisplatin ineligible patients), for first-line treatment in patients with unresectable malignant pleural mesothelioma.	×	×	×	×	×	×	×	×	×

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan.

(✓ funded; ² funded on case-by-case basis; †under negotiations with manufacturer or under consideration by province; × not funded).

The information was validated and supplemented by the member representatives of the CADTH pCODR Provincial Advisory Group.

	BC	AB	SK	MB	ON	NS	NB	NL	PEI
Rituximab (Rituxan)									
Non-Hodgkin Lymphoma: relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.	✓	✓	✓	✓	×	✓	✓	✓	✓
Non-Hodgkin Lymphoma: CD20 positive, diffuse large B-cell non-Hodgkin lymphoma (DLBCL) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-Hodgkin Lymphoma: previously untreated Stage III/IV follicular, CD20 positive, B-cell non-Hodgkin lymphoma in combination with CVP (cyclophosphamide, vincristine, and prednisolone) chemotherapy.		✓	✓	✓	✓	✓	✓	✓	✓
Non-Hodgkin Lymphoma: the maintenance treatment of follicular non-Hodgkin lymphoma who have responded to induction therapy with either CHOP or CHOP plus Rituxan		✓	✓	✓	✓	✓	✓	✓	✓

	BC	AB	SK	MB	ON	NS	NB	NL	PEI
Non-Hodgkin Lymphoma: single-drug maintenance treatment of previously untreated advanced follicular non-Hodgkin lymphoma with high tumour burden and who have responded to induction therapy with either CHOP plus Rituxan or CVP plus Rituxan.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chronic Lymphocytic Leukemia (CLL): previously untreated B-cell chronic lymphocytic leukemia (B-CLL), Binet Stage B or C, in combination with fludarabine and cyclophosphamide.	✓	✓	✓	✓	2	✓	✓	✓	✓
Chronic Lymphocytic Leukemia (CLL): previously treated B-cell chronic lymphocytic leukemia (B-CLL), Binet Stage B or C, in combination with fludarabine and cyclophosphamide.	1	✓	✓	✓	2	✓	✓	✓	×
BMT up to 4 cycles of rituximab-based salvage therapy as a bridge before transplant,	×	✓		✓		×		✓	
Hodgkin Lymphoma: In combination with chemotherapy for the treatment of patients with CD20+ve, lymphocyte predominant disease.	×	✓	✓		×		✓	✓	✓
Indolent Non-Hodgkin Lymphoma and Mantle Cell Lymphoma: in combination with bendamustine, for first-line and relapsed/ refractory.	✓	✓	✓	✓		✓		✓	
Chronic Lymphocytic Leukemia (CLL): relapsed/refractory, in combination with bendamustine.	✓	✓	×	×		×		✓	
Chronic Lymphocytic Leukemia (CLL): first-line treatment, in combination with bendamustine.	✓	✓	✓	✓		×		✓	
Chronic Lymphocytic Leukemia (CLL): in combination with idelalisib.	†	✓	✓		✓		✓		†

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(✓ Funded; ² funded on case by case basis; †under negotiations with manufacturer or under consideration by province; × Not funded)

[1] fludarabine + rituximab without cyclophosphamide

[2] fludarabine + rituximab with or without cyclophosphamide

The information was validated and supplemented by the member representatives of the CADTH pCODR Provincial Advisory Group.

	BC	AB	SK	MB	ON	NS	NB	NL	PEI
Trastuzumab (Herceptin)									
Early breast cancer: for the treatment of patients with early stage breast cancer with ECOG 0-1 status, whose tumours overexpress HER2: • following surgery and after chemotherapy • following adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel • in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Metastatic breast cancer (MBC): for the treatment of patients with MBC whose tumours overexpress HER2.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Metastatic breast cancer (MBC): in combination with PERJETA (pertuzumab) and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	✓	✓	✓	✓	✓	✓	✓	✓	✓
Metastatic Gastric Cancer: in combination with capecitabine or intravenous 5-fluorouracil and cisplatin, for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.	✓	✓	✓	✓	✓	×	✓	✓	×

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PEI = Prince Edward Island; SK = Saskatchewan.

(✓ Funded; ² funded on case by case basis; †under negotiations with manufacturer or under consideration by province; × Not funded)

The information was validated and supplemented by the member representatives of the CADTH pCODR Provincial Advisory Group

Limitations

The findings of this Environmental Scan are based on a limited literature search and a survey sent to selected HTA organizations. The policies, procedures, and guidelines on biosimilar market access and uptake are rapidly evolving, and therefore, the details within are current up to the dates indicated throughout the report.

Conclusion

Health Canada, the FDA, and the EMA all follow similar scientific principles in their regulatory guidelines for biosimilars. The EMA has been a global leader in establishing the regulatory frameworks for biosimilars, and currently the EU has the most biosimilars on the market. The key differences between the regulators relate to guidance on interchangeability, and the naming and labelling conventions for biosimilars.

The approaches taken by HTA agencies vary. Different countries also use different sets of context-specific strategies for biosimilar pricing and reimbursement. It is not possible to identify a single best biosimilar policy. However, since many stakeholders are involved in the market access and uptake of biosimilars, it seems that a mix of interventions and active stakeholder collaboration are needed to support successful biosimilar uptake. Also interventions to increase patient and physician acceptance are essential.

Many of the top selling biologic drugs already have or are expected to have biosimilars enter the market within the next few years. The European experience shows that increased biosimilar competition has not only affected the prices of the directly comparable biosimilars and their reference product, but also of the whole product class. In addition, the pharmaceutical industry uses a variety of strategies, such as extending patents and product evergreening (e.g., introducing a new formulation for reference product), to mitigate the decline in revenue after the patent expiration of reference products. To best optimize the biosimilar price competition, HTA, and reimbursement and pricing organizations may wish to consider the therapeutic and economic value of biosimilars not only against the directly comparable reference products, but also against the whole therapeutic class.

Complementing this Environmental Scan, CADTH has prepared handouts for patients and health care providers designed to share information on biosimilar drugs. These handouts are available free of charge on the CADTH website (https://cadth.ca/biosimilar-drugs).

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Appendix A: Email Survey

Dear XXXXX,

We are writing to request your participation in **CADTH's Environment Scan on Biosimilars — Regulatory, HTA, Reimbursement Trends, and Market Outlook.**

The aim of the Environmental Scan is to identify and compare the regulatory frameworks, HTA processes, and reimbursement trends of national and international organizations and to describe the market outlook of biosimilars and their reference products in Canada.

In order to ensure that we present the most up-to-date and accurate information, we are interested in your responses to the following questions:

1. Does your organization review biosimilars?

   a) If no, is another organization responsible for the HTA process of biosimilars in your country?

2. If your organization does review biosimilars, is your process the same as the regular review process that is followed for new drugs in the context of a single technology assessment?

   a) If yes, could you share with us any documents that would outline the process?

   b) If no, could you briefly describe what is different in: (i) the evidence appraisal (clinical and economic review), and (ii) reimbursement recommendations or decision-making. Could you share with us any documents that would outline the differences in the process?

3. Does your organization have a position statement on interchangeability, switching and/or substitution of biosimilars?

   a) If yes, could you share with us any documents that would outline your position statement?

Please note that the information contained in any documents provided must be disclosable.

We would greatly appreciate if you could respond by ___[*INSERT DATE*]__.

Please note that your response to the survey will be used to prepare a CADTH Environment Scan Report which will be available for public access. Please insert (type) your first and last name on the line within the disclaimer provided below in red, to authorize CADTH to use the information provided by you in the Environmental Scan report. Note that this consent does not give CADTH permission to disclose your name within the report.

This information is provided to assist CADTH in conducting the Environmental Scan entitled Environment Scan on Biosimilars - *Regulatory, HTA, Reimbursement Trends, and Market Outlook*. By responding to this survey, I — _____ — give my authorization for CADTH to summarize my responses in the published Environmental Scan report and for my organization to be identified as a source for survey respondents. However, I (and the organization I represent) decline any responsibility for the analyses, conclusions, opinions, and statements expressed in CADTH's Environmental Scan report.

Thank you in advance for your time and consideration,

Appendix B: Definitions

Biosimilar / biosimilarity	**Health Canada:** Biosimilar is a biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. Biosimilar biologic drugs were previously referred to as Subsequent Entry Biologics in Canada. **FDA:** Biosimilar or biosimilarity means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. **EMA:** A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established. **TGA:** A biosimilar medicine is a version of an already registered biological medicine (the reference medicine). **Medsafe:** A biosimilar medicine is a new biological product that is similar to another biological medicine that has been granted consent to be marketed in New Zealand (the biological reference).
Reference product	**Health Canada:** Reference biologic drug is a biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which a biosimilar is compared with to demonstrate similarity. **FDA:** Reference product means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application. **EMA:** Reference medicine is a biological medicine approved in the EU, which is chosen by a company developing a biosimilar as a reference for the head-to-head comparison of quality, safety and efficacy. **TGA:** The reference medicine must be a biological medicine that has been registered in Australia based on full quality, safety and efficacy data ('the Australian reference medicine'). In addition, the Australian reference medicine must have been marketed in Australia for a substantial period and have a volume of marketed use so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications. **Medsafe:** The chosen reference product must be an innovator biological medicine that has consent for distribution in New Zealand.
Extrapolation	**EMA:** Extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication approved for the reference medicine."
Interchangeability	**Health Canada:** Ability for a patient to be changed from one drug to another equivalent drug by a pharmacist, without the intervention of the doctor who wrote the prescription. **FDA:** The biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. **EMA:** The possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by substitution or switching.
Switching	**Health Canada:** One-time change from a reference biologic drug to a biosimilar. **EMA:** When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
Substitution	**EMA:** Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

EMA = European Medicines Agency, TGA = Therapeutic Goods Administration.

Source: Health Canada;[19] FDA;[29] EMA and European Commission;[20]Therapeutic Goods Administration;[24] Medsafe.[23]

Appendix C: CADTH Reimbursement Recommendations for Biosimilars

Currently seven biosimilars are authorized in Canada: Brenzys (etanercept), Erelzi (etanercept), Grastofil (filgrastim), Inflectra (infliximab), Remsima (infliximab), Basaglar (insulin glargine), and Omnitrope (somatropin). The CADTH reimbursement recommendations for these products are reported in Table 13. In general, CADTH's Canadian Drug Expert Committee (CDEC) has recommended listing biosimilars in accordance with the approved indications, in a manner similar to the reference product and with cost considerations.

CDEC has commented on switching in some of their recommendations on biosimilars (Table 13). For Basaglar (insulin glargine) and Grastofil (filgrastim), CDEC has noted that a patient being treated with the reference product should be considered for switching to the biosimilar, following a discussion between the patient and their physician.

Table 13: Biosimilars Currently Marketed in Canada and CADTH Reimbursement Recommendations

Active substance (brand name)	Indications	Recommendation by CDEC (year issued)	Criteria or Conditions for the Recommendation	"Of Note" Related to Switching
Omnitrope **(Somatropin)**	Growth hormone deficiency in children and adults	Advice (2009)	The Canadian Expert Drug Advisory Committee's (CEDAC's) advice on Omnitrope is that drug plans consider a similar reimbursement policy for Omnitrope as for other growth hormone products.	Of Note: There is no evidence of the effect of switching between Omnitrope and other Canadian growth hormone products on outcomes.
Inflectra **(Infliximab)**	Ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis	LWCC (2014)	Conditions: For use in patients for whom infliximab is considered to be the most appropriate treatment option. List in a manner similar to Remicade.	No "Of Note".
Inflectra **(Infliximab)**	Crohn's disease fistulizing Crohn's disease, ulcerative colitis (UC)	LWCC (2016)	Clinical Criterion: For use in patients for whom infliximab is considered to be the most appropriate treatment option. Conditions: Reimburse in a manner similar to Remicade. The cost of treatment with Inflectra should provide a significant cost savings for jurisdictions compared with the cost of treatment with Remicade.	No "Of Note".

Active substance (brand name)	Indications	Recommendation by CDEC (year issued)	Criteria or Conditions for the Recommendation	"Of Note" Related to Switching
Basaglar **(Insulin Glargine)**	Diabetes, Type 1 & 2	LWCC (2016)	Conditions: List in a similar manner to the public plan listing criteria for Lantus. The cost of treatment with Basaglar should provide significant cost savings for jurisdictions compared with the cost of treatment with Lantus.	Of Note: CDEC noted that a patient being treated with Lantus should be considered for switching to Basaglar, following a discussion between the patient and his or her physician.
Grastofil **(Filgrastim)**	Prevention or treatment of neutropenia in various indications	LWCC (2016)	Conditions: List in a manner similar to Neupogen The cost of treatment with Grastofil should provide significant cost savings for jurisdictions compared with the cost of treatment with Neupogen.	Of Note: CDEC noted that a patient being treated with Neupogen should be considered for switching to Grastofil, following a discussion between the patient and his or her physician.
Brenzys **(Etanercept)**	Rheumatoid arthritis, ankylosing spondylitis	LWCC (2016)	Clinical Criterion: For use in patients for whom etanercept is considered to be the most appropriate treatment option. Conditions: Reimburse in a manner similar to Enbrel. The cost of treatment with Brenzys should provide significant cost savings for jurisdictions compared with the cost of treatment with Enbrel.	Of Note: An open-label extension phase of study SB4-G31-RA suggested that there were no efficacy, safety, or tolerability concerns in patients who either remained on Brenzys or were switched from Enbrel to Brenzys, after the double-blind phase of the study. These results, however, were not compared statistically to a group of patients who remained on Enbrel.

Active substance (brand name)	Indications	Recommendation by CDEC (year issued)	Criteria or Conditions for the Recommendation	"Of Note" Related to Switching
Erelzi **(Etanercept)**	Ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis	LWCC (2017)	Criterion: For use in patients for whom etanercept is considered to be the most appropriate treatment option. Conditions: Reimburse in a manner similar to Enbrel. The cost of treatment with Erelzi should provide significant cost savings for jurisdictions compared with the cost of treatment with existing etanercept products.	Of Note: Results from the 18-week treatment crossover period and the 22-week extension phase of EGALITY suggest that switching from Enbrel to Erelzi and vice versa can be performed safely without any loss of efficacy.

CDEC = CADTH Canadian Drug Expert Committee; CEDAC = CADTH Canadian Expert Drug Advisory Committee (the predecessor to CDEC); LWCC = list with criteria and/or conditions.

Appendix D: The 30 top Selling Biologic Drugs, Canada, 2016*

Rank	Molecule (product[a])	Molecule Share of Pharmaceutical Sales[b] (2016), %	First[c] Notice of Compliance[d]
1	**Infliximab** (Remicade, **Inflectra**)	4.4	2001
2	Adalimumab (Humira)	2.9	2004
3	**Etanercept** (Enbrel, **Brenzys**)	1.5	2000
4	Ranibizumab (Lucentis)	1.5	2007
5	**Insulin Glargine** (Lantus Solostar, Lantus, Toujeo Solostar, **Basaglar**)	1.1	2002
6	Trastuzumab (Herceptin, Perjeta & Herceptin)	1.1	1999
7	Rituximab (Rituxan, Rituxan SC)	1.1	2000
8	Aflibercept (Eylea, Zaltrap)	1.1	2013
9	Ustekinumab (Stelara)	0.8	2008
10	Vaccine, Varicella Zoster (Zostavax II, Proquad, Varivax III, Priorix-Tetra, Varilrix)	0.6	1997
11	**Filgrastim** (Neupogen, **Grastofil**)	0.6	1992[e]
12	Golimumab (Simponi, Simponi IV)	0.6	2009
13	Denosumab (Prolia, Xgeva)	0.5	2010
14	Liraglutide (Victoza, Saxenda)	0.5	2010
15	Darbepoetin Alfa (Aranesp)	0.5	2002
16	Omalizumab (Xolair)	0.5	2004
17	Dalteparin Sodium (Fragmin)	0.5	1994
18	Bevacizumab (Avastin)	0.5	2005
19	Interferon Beta-1A (Rebif, Avonex)	0.5	1998
20	Epoetin Alfa (Eprex)	0.4	1990[e]
21	Insulin Aspart (Novorapid, Novomix 30, Novarapid Flextouch)	0.4	2001
22	Insulin Lispro (Humalog, Humalog Mix 25, Humalog Mix 50)	0.4	1996
23	Insulin Detemir (Levemir, Levemir Flextouch)	0.3	2005
24	Pegfilgrastim (Neulasta)	0.3	2004
25	Insulin Human Isophane (Novolin ge NPH, Humulin N, Novolin ge 30/70, Humulin 30/70, Novolin ge 50/50, Novolin ge 40/60)	0.3	1996
26	Abatacept (Orencia)	0.3	2006
27	Vaccine, Human Papillomavirus (HPV) Type-6,11,16 & 18 (Gardasil)	0.2	2006
28	Natalizumab (Tysabri)	0.2	2006
29	Alteplase (Cathflo, Activase)	0.2	1994
30	Tocilizumab (Actemra)	0.2	2010
	Somatropin (Humatrope, Saizen Liquid, **Omnitrope**, Nutropin Aq Nuspin, Saizen, Nutropin Aq, Genotropin, Serostim, Norditropin Nordif)	0.2	1987[e]

[a] Products are listed in descending order by the pharmaceutical sales.

[b] Source: QuintilesIMS MIDASTM Database 2016, share of the prescription market. Includes all products listed.

[c] For any of the products listed.

[d] Source: Health Canada Notice of Compliance Database.

[e] Source: QuintilesIMS MIDAS™ Database 2016.

Note: Bold font is used to indicate biosimilars approved in Canada as of May 31, 2017.

*Data Source: Patented Medicine Prices Review Board analysis of the MIDAS™ Database, 2016. QuintilesIMS. All rights reserved.

Appendix E: CADTH Reimbursement Recommendations for Selected Reference Products

Table 14: CADTH Reimbursement Recommendations for Top Selling Oncology Reference Products

Product (active substance)	Funding Request	CADTH pERC Recommendation (year issued)	Link to the Recommendation
Avastin (Bevacizumab)	In combination with chemotherapy for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix.	Reimburse with conditions/criteria (2015)[98]	https://www.cadth.ca/sites/default/files/pcodr/pcodr-avastincc-fn-rec.pdf
Avastin (Bevacizumab)	In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients.	Reimburse with conditions/criteria (2015)[99]	https://www.cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_oc-fn_rec.pdf
Avastin (Bevacizumab)	In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Reimburse with conditions/criteria (2016)[100]	https://www.cadth.ca/sites/default/files/pcodr/pcodr_bevacizumab_avastin_proc_fn_rec.pdf
Avastin (Bevacizumab)	In combination with pemetrexed and cisplatin or carboplatin (for cisplatin ineligible patients), for first-line treatment in patients with unresectable malignant pleural mesothelioma.	The marketing authorization holder requested a voluntary withdrawal of the submission[101]	
Avastin (Bevacizumab)	In combination with capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (CRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy.	Reimburse with conditions/criteria (2016)[102]	https://www.cadth.ca/sites/default/files/pcodr/pcodr_avastin_capecitabine_mcrc_fn_rec.pdf
Rituxan (Rituximab)	In combination with standard of care chemotherapy for Philadelphia chromosome negative, CD20 antigen positive, B-cell precursor acute lymphoblastic leukemia in adults.	Under review[103]	

Table 15: CADTH Reimbursement Recommendations for Top Selling Non-Oncology Reference Products

Active substance	Indications	CDEC Recommendation (year issued)	Criteria or Conditions for the Recommendation[1]	Link to the Recommendation
Remicade (Infliximab)	Ulcerative colitis	DNL (2009)[104]	Not applicable	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Remicade_Final_April_24_2009.pdf
Humira (Adalimumab)	Rheumatoid arthritis	LWCC (2005)[105]	• Reimbursement of the drug in a manner similar to comparator(s) • Reimbursement limits • Not in combination other anti-TNF agents	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira%28adalimumab%29Feb11-05.pdf
Humira (Adalimumab)	Psoriasis	LWCC (2008)[106]	• Clinical criteria • Starting/stopping rules • Maximum dose	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-Psoriasis_October_2008.pdf
Humira (Adalimumab)	Arthritis, juvenile idiopathic	LWCC (2013)[107]	• Starting/stopping rules • Treatment should be initiated by experienced rheumatologist	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-JIA_July-22-13_e.pdf
Humira (Adalimumab)	Arthritis, psoriatic	LWCC (2006)[108]	• Clinical Criteria • Starting/stopping rules • Maximum dose	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira_Resubmission_Nov29-06.pdf
Humira (Adalimumab)	Ankylosing spondylitis	LWCC (2007)[109]	• Clinical criteria • Reimbursement of the drug in a manner similar to comparator(s) • Starting/stopping rules • Maximum dose • Not in combination other anti-TNF agents.	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira_Resubmission_June-27-2007.pdf
Humira (Adalimumab)	Crohn's Disease in adults	LWCC (2007)[110]	• Clinical criteria • Starting/stopping rules • Reimbursement limits • Maximum dose	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-Resubmission-Crohns_Dec-19-2007.pdf
Humira (Adalimumab)	Ulcerative colitis	DNL at the submitted price (2016)[111]	Not applicable	https://www.cadth.ca/sites/default/files/cdr/complete/SR0450_complete_Humira-Apr-19-16_e.pdf

Active substance	Indications	CDEC Recommendation (year issued)	Criteria or Conditions for the Recommendation[1]	Link to the Recommendation
Humira (Adalimumab)	Hidradenitis suppurativa	LWCC (2016)[112]	• Clinical criteria • Starting/stopping rules • Under the care of experienced physician • Cost considerations	https://www.cadth.ca/sites/default/files/cdr/complete/SR0455_complete_Humira-HS_May-24-16_e.pdf
Lucentis (Ranibizumab)	Macular degeneration, age-related	LWCC (2008)[113]	• Reimbursement limits	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Lucentis_March-27-2008.pdf
Lucentis (Ranibizumab)	Macular edema, diabetic	LWCC (2012)[114]	• Clinical criteria • Reimbursement limits	https://www.cadth.ca/sites/default/files/cdr/complete/cdr-complete_Lucentis_DME_March-21-12.pdf
Lucentis (Ranibizumab)	Macular edema, secondary to retinal vein occlusion	LWCC (2012)[115]	• Clinical criteria • Reimbursement limits	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Lucentis%20RVO_Oct-22-12_e.pdf
Lucentis (Ranibizumab)	Choroidal neovascularization, myopic	LWCC (2015)[116]	• Cost considerations	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0373_Lucentis_CNV_Feb-20-15.pdf
Rituxan (Rituximab)	Rheumatoid arthritis	LWCC (2007)[117]	• Clinical criteria • Not in combination other anti-TNF agents.	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Rituxan_Feb14-2007.pdf
Rituxan (Rituximab)	Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA), remissioninduction (adults)	LWCC (2012)[118]	• Clinical criteria	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Rituxan-Aug_16-12_e.pdf
Lantus (Insulin glargine)	Diabetes mellitus, Type 1 & 2	DNL (2006)[119]	Not applicable	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Lantus_Oct25-06.pdf
Neulasta (Pegfilgrastim)	Neutropenia	LWCC (2004)[120]	• Clinical criteria	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_neulasta_10-27-04.pdf
Xolair (Omalizumab)	Asthma, severe persistent	LWCC (2015)[121]	• Clinical criteria • Under the care of experienced physician • Cost considerations	https://www.cadth.ca/sites/default/files/cdr/complete/SR0457_complete_Xolair_Resub-May_19_16.pdf

Active substance	Indications	CDEC Recommendation (year issued)	Criteria or Conditions for the Recommendation[1]	Link to the Recommendation
Xolair (Omalizumab)	Urticaria, chronic idiopathic	LWCC (2015)[122]	• Clinical criteria • Cost considerations • Reimbursement limits	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0398_Xolair-CIU_May-11-15.pdf
Tysabri (Natalizumab)	Multiple Sclerosis, relapsing-remitting	LWCC (2009)[123]	• Clinical criteria	https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Tysabri-Resubmission_February-25-2009.pdf

CDR = CADTH Common Drug Review; DNL = do not list; LWCC = list with criteria and/or conditions; MAH = marketing authorization holder; pCODR = CADTH pan-Canadian Oncology Drug Review.

[1] Examples of criteria and conditions:

Clinical criteria: inability to use, intolerance, or inadequate response to appropriate comparator(s); severity of disease or disease progression.

Stopping rules: duration of treatment, response to treatment.

Cost considerations: reduction in price.

Reimbursement limits: number of dose.

Appendix F: Federal, Territorial, and Provincial Drug Programs Funding Summary for Selected Biologic Drugs for Non-oncology Indications

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[124]
Humira (adalimumab)													
Rheumatoid arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
Polyarticular juvenile idiopathic arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	not a benefit	not a benefit
Psoriatic arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
Ankylosing spondylitis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
Adult Crohn'sdisease	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
Pediatric Crohn's disease	RES	not a benefit		RES	RES	RES	not a benefit	case by case	RES	RES	RES	not a benefit	not a benefit
Ulcerative colitis	RES	UR	RES	not a benefit	not a benefit	not a benefit	RES	RES	not a benefit	RES	RES	not a benefit	not a benefit
Hidradenitis suppurativa	not a benefit	UR	EX	not a benefit	not a benefit	not a benefit	UR	UR	not a benefit	RES	not a benefit	not a benefit	not a benefit
Plaque psoriasis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
Uveitis	not a benefit	not a benefit	EX	not a benefit	RES	not a benefit	not a benefit	RES	not a benefit	RES	not a benefit	not a benefit	not a benefit
Lucentis (ranibizumab)													
Macular degeneration, age-related	Available through retinal program	RES	RES	RES	RES	RES (in hospital clinics)	RES	RES	RES	RES	RES	RES	RES
Macular edema, diabetic		RES	RES	RES	RES		RES	RES	not a benefit	RES	RES	not a benefit	RES
Macular edema, secondary to retinal vein occlusion		RES	RES	RES	RES		UR	RES	not a benefit	RES	RES	not a benefit	RES
Choroidal neovascularization, myopic		UR	RES	not a benefit	RES		UR	UR	not a benefit	RES	RES	RES	RES
Rituxan (rituximab)													
Rheumatoid arthritis	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
GPA or MPA	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	not a benefit	RES

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[124]
Lantus (insulin glargine)													
Diabetes, Type 1 & 2	RES	FB	FB	RES	FB	RES	RES	RES	RES	RES	FB	FB	FB
Pediatric diabetes Type 1	RES			RES		RES	RES		RES	RES			
Basaglar (insulin glargine-biosimilar)													
Diabetes, Type 1 & 2	UR	UR	UR	not a benefit	FB	UR	UR	UR	FB	FB	UR	FB	not a benefit
Pediatric diabetes Type 1	UR	UR	UR	not a benefit		UR	UR	UR					
Neupogen (filgrastim)													
Congenital, cyclic or idiopathic neutropenia	not a benefit	RES	RES	RES	not a benefit	RES (hospital program)	not a benefit	not a benefit	not a benefit	RES	FB	FB	RES
Neutropenia in HIV	through Centre of Excellence	not a benefit	RES	RES	RES		not a benefit	not a benefit	not a benefit	RES			
Grastofil (filgrastim-biosimilar)													
Congenital, cyclic or idiopathic neutropenia	RES	RES	RES	RES	FB	UR (hospital program)	RES	not a benefit	RES	RES	FB	FB	not a benefit
Neutropenia in HIV	through Centre of Excellence	not a benefit	RES	RES			RES	not a benefit	RES	RES			
Xolair (omalizumab)													
Asthma, severe persistent	not a benefit	RES	EX	not a benefit	RES	not a benefit	UR	not a benefit	not a benefit	RES	not a benefit	UR	not a benefit
Urticaria, chronic idiopathic	not a benefit	UR	RES	not a benefit	not a benefit	RES	RES	RES	not a benefit	RES	RES	RES	
Eprex (epoetin alfa)													
Anemia in several indications	not a benefit	RES	RES	RES	RES	RES	RES	FB/RES	RES	RES	RES	FB	RES
Aranesp (Darbepoetin)													
Anemia in kidney disease or due to chemotherapy	not a benefit	RES	RES	RES	RES	RES	RES	FB/RES	RES	RES	RES	FB	RES

Health Canada Approved Indications	BC[70,71]	AB[72]	SK[73,74]	MB[75,76]	ON[77]	NS[78,79]	NB[80]	NL[81]	PEI[82]	YK[83]	NIHB[84]	CAF[85]	VAC[124]
Tysabri (Natalizumab)													
Multiple sclerosis, relapsing-remitting	RES	RES	RES	RES	RES	RES	RES	not a benefit	not a benefit	RES	not a benefit	RES	RES

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; EDS = exceptional drug status; EX = exception item for which coverage is determined on a case-by-case basis; FB = full benefit; GPA = granulomatosis with polyangiitis; LU = limited use program; MB = Manitoba; MPA = microscopic polyangiitis; NB = New Brunswick; NIHB = Non-Insured Health Benefits plans; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; RES = restricted benefit with specified criteria (special authorization, exception drug status, limited use benefit); pCPA = pan-Canadian Pharmaceutical Alliance; PEI = Prince Edward; SA = special authorization; SK = Saskatchewan; UR = under review; VAC = Veterans Affairs Canada; YK = Yukon.