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BIOLOGICS AND BIOSIMILARS
A PRIMER

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Contents

Executive Summary

Biological products (biologics) comprise the cutting edge of medical science and biomedical research, replicating natural substances such as enzymes, antibodies or hormones. Biologics are made from a variety of natural resources—human, animal, and microorganism—and can be composed of sugars, proteins, or nucleic acids, or a combination of these substances. The pharmaceutical industry has been revolutionized by the development of biologic medicines. Both the creation and the regulation of biologic medicines differ in important ways from traditional so-called "small molecule" drugs.

Biologics cost more to develop and manufacture than do small molecule drugs. In addition, they also require more time to bring to market, an average of 10 to 15 years as compared to 7 to 10 years for a small molecule drug. In addition, while a typical manufacturing process for a small molecule drug might require 40-50 critical tests, the process for a biologic medicine may include 250 or more.

In order to satisfy Health Canada, a biosimilar must demonstrate that it is "highly similar" to the reference product, and that there are no "clinically meaningful differences in terms of safety and efficacy between them." Health Canada uses a "totality of the evidence" approach to demonstrate biosimilarity to the reference product and evaluate applications for biosimilar products.

Biologic medicines have many more places for variation than small molecule drugs. As a consequence, even slight irregularities may potentially alter how patients respond. Slight differences in biologic medicines may result in reduced efficiency or induce immunogenic responses. These complications may even occur when the original manufacturer makes slight known changes (evolution) or unknown changes (drift) to its own production process, which can then yield a product that diverges from its predecessor. As a result, regulatory authorities require far more extensive testing for biosimilars relative to generic drug products.

Numerous studies have shown that the introduction of generic versions of small molecule pharmaceutical can reduce prices by 90 percent relative to the branded version. Similar savings cannot be expected from

biosimilars. Given that they are only similar to the originator biologics, the biosimilars will require their own lengthy and expensive clinical trials in order to ensure that they are safe and effective. Then, after that expensive testing, biosimilars are expected to reduce prices by a more modest 20 to 30 percent.

Canada's protection of intellectual property in the life sciences significantly lags behind that provided by many other industrialized nations, including the United States, the EU and Japan. Canada currently has one of the shortest terms of data exclusivity for pre-clinical and clinical trials. Canada's unique misinterpretation of the utility standard is also a significant barrier to biopharmaceutical innovation.

This study introduces biologic medicines and biosimilars and explores some of the challenges and controversies that uniquely characterize their production, regulation, and marketing. The primer presents an overview of the basics of biologics and biosimilars, and discusses how biologics differ from traditional small molecule pharmaceuticals. It also explores the differences between biosimilars and traditional generic drugs. Emphasizing the importance of precision in biologic development and manufacture, the study considers salient features of production and market characteristics. In addition, the study focuses on the market failures present in the biopharmaceutical industry and the role of intellectual property rights in ensuring that the promise of biologic medicine is realized. Finally, the paper describes the Canadian specifics for the biopharmaceutical industry. Understanding both the promise and the challenges of biologic medicines is valuable for patients and policymakers alike. If we are to realize the benefits of these therapeutic advances, we must ensure that there are sufficient incentives in place for manufacturers to develop them, and that they are developed precisely, manufactured responsibly, and effectively brought to those who need them.

Introduction

Biological products (biologics) comprise the cutting edge of medical science and biomedical research, replicating natural substances such as enzymes, antibodies or hormones. "Biological products can be composed of sugars, proteins, or nucleic acids, or a combination of these substances. They may also be living entities, such as cells and tissues. Biologics are made from a variety of natural resources—human, animal, and microorganism—and may be produced by biotechnology methods" (FDA, 2008). The development of biologic medicines has revolutionized the pharmaceutical industry. Biologics are transforming the lives of patients across the globe, and they are poised to become ever more important in the years to come. Both the creation and the regulation of biologic medicines differ in important ways from traditional so-called "small molecule" drugs.

Biopharmaceuticals are currently produced using one of two technology platforms and the active chemical substances in them can be classified as "large molecules" and "small molecules." Historically, pharmaceuticals have been small, chemically manufactured molecules. These molecules still comprise more than 90 percent of drugs currently available. Small molecule therapies are synthesized through chemical reactions between different organic and/or inorganic compounds. In comparison, biologics, or large molecules, are therapeutic proteins and are most often derived from living cells (Bayer Health Care, n.d.). Biologics are produced from micro-organisms or animals by using the metabolic processes of the organisms themselves. Biologics include insulin, monoclonal antibodies, vaccines, blood and blood products, protein hormones, cellular therapies, allergenic extracts, and gene therapy products. Examples of biologics include: adalimumab (Humira), trastuzumab (Herceptin), etanercept (Enbrel), bevacizumab (Avastin), and rituximab (Rituxan) (Lybecker, 2014; Lybecker, 2016). The differences and how they are addressed are of critical importance in determining the future of health care and the treatment patients will receive for decades to come (Lybecker, 2016).

The term "biotechnology" first appeared in 1919, describing "the interaction between biology and human technology for conversion of

raw materials into socially valuable products" (Amgen, 2014: 3). Early on, the focus of biotechnology shifted from primarily food production to the development of medicines. By the early 1940s, humanity was benefitting from the mass production of antibiotics, and in the early 1950s, the structure of DNA was discovered, laying the groundwork for modern biotech advances in medicine. Nevertheless, a consensus on the meaning of biotechnology was not reached until the United Nations and World Health Organization accepted the 1992 Convention on Biological Diversity. Under Article 16 of the convention, biotechnology is defined as "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" (United Nations, 1992).

The distinctive characteristics required for the development and production of biologic medicines raise significant policy issues and highlight many of the most contentious issues in the debates over their use and protection. For example, the question of how much data exclusivity should be accorded to patented biologics has been raised in the negotiations of the amended United States–Mexico–Canada Agreement (USMCA or CUSMA). In addition, there is discussion surrounding whether new biologics are worth their cost and how governments and private insurers should assess the social value of new biologic medicines.

This paper is intended as a primer to biologic medicines, biosimilars,[1] and to some of the issues and controversies that are unique to their production, regulation, and marketing. The study begins with definitions of the terms used in the paper, continues with an overview of the basics, and then discusses how biologics differ from traditional small molecule pharmaceuticals. The primer also explores the differences between biosimilars and traditional generic drugs. Emphasizing the importance of precision in biologic development and manufacture, the study considers salient features of production and market characteristics. In addition, it focuses on the market failures present in the biopharmaceutical industry and the role of intellectual property rights in ensuring that the promise of biologic medicine is realized. Finally, the paper describes the Canadian specifics for the biopharmaceutical industry.

Understanding both the promise and the challenges of biologic medicines is valuable for patients and policymakers alike. Policy-oriented readers of all types will find this piece instructive and laced with scientific

[1] Biosimilars are frequently compared to the generic version of traditional small-molecule drugs. While biosimilars are subsequent entrants to the market, they differ in important ways from generic drugs. Most significantly, generic drugs are chemically identical to their reference innovator products, while biosimilars are never identical and may only be established to be "highly similar".

details surrounding the discovery, production, and protection of biologic medicines. This context is valuable for several reasons: (1) it provides a starting point for those who wish to delve more deeply into the issues, (2) it provides precise evidence to back up the claims that are made, and (3) it is essential for a complete understanding of the relatively high costs of biologic drugs. If we are to realize the benefits of these therapeutic advances, we must ensure that there are sufficient incentives in place for manufacturers to develop them, and that they are developed precisely, manufactured responsibly, and effectively brought to those who need them.

Definitions

> "The difference between the almost right word and the right word is a really large matter – it is the difference between the lightning bug and the lightning."
> —Mark Twain, as quoted by Morrow and Felcone (2004)

Indeed, in the context of medicines, and biologic medicines in particular, definitions and "the right word" are critically important. Given this, this study begins by discussing the definitions of biologics and biosimilars and describing the distinctions between them, traditional small molecule medicines, and generic drugs. Table 1 identifies the important distinctions between biologics and small molecule drugs.

Table 1: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Pharmaceuticals	Biologics
Method of Synthesis	Chemical synthesis	Genetically engineering living organisms or cells; bacterial or mammalian
Molecular Size	Small	Large
Structure	Usually fully known	Complex, frequently partially unknown
Susceptibility to Contamination during Manufacturing	Low	High
Uniformity	Single substance	Mixture of variants
Molecular Structure	Relatively simple spatial structures, determined through analytical technology	Exhibit complex spatial structures, difficult to determine
Complexity	Relatively pure ingredients	Complex ingredients (impurities, leachables, excipients, by-products)

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Table 1: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Pharmaceuticals	Biologics
Sensitivity to Physical Factors (heat, light)	Low	Higher
Clinical Behavior	Well understood mode of action	Complicated modes of action, not always well understood
Manufacturing Process	Straightforward, relatively simple	Highly complex
Species	Interdependent	Specific
Immunogenicity	Non antigenic (generally)	Antigenic (MW>10kDa)
ADME[1]		
Absorption	Faster	Slower
Distribution	High	Low/Limited
Metabolism	Metabolized to non-active and active metabolites	Catabolized to endogenous amino acids
Disposition	Rarely targeted-mediated	Often target-mediated
PK Profile[2]	Frequently Linear	Usually Non-linear
Half-life	Short(er)	Long
Safety	Toxicity (variable mechanisms)	Exaggerated pharmacology[3]
Testing	40-50 times during production	250 time or more during production
Example	Aspirin	Bevacizumab (MAB: Monoclonal Antibody)
Average Cost in the US per day	$2 (US)	$45 (US)

Sources: Klein and Wang, 2013; Lybecker, 2014; Lybecker, 2016; IGBA, n.d.(a); Boehringer Ingelheim, 2019; Blackstone and Fuhr, 2013.

[1] ADME: Absorption, Distribution, Metabolism, and Excretion.

2 Pharmacokinetics, sometimes abbreviated PK, is the branch of pharmacology devoted to the study of the fate of pharmacological substances in the body, specifically, how they are absorbed, distributed, metabolized, and eliminated. "When the dose of a drug is increased, we expect that the concentration at steady state will increase proportionately, i.e. if the dose rate is increased or decreased say two-fold, the plasma drug concentration will also increase or decrease two-fold. However, for some drugs, the plasma drug concentration changes either more or less than would be expected from a change in dose rate. This is known as non-linear pharmacokinetic behaviour and can cause problems when adjusting dose." (Birkett, 1994: 36).

3 Biologics toxicity typically manifests as exaggerated pharmacology, though there are some reported cases of unexpected toxicity. "Exaggerated pharmacology" is toxicity resulting from excessive modulation of the activity of the primary pharmacological target. "Adverse toxicologic effects are categorized as chemical-based, on-target (also referred to as target-related, exaggerated pharmacology or mechanism-based), or off-target effects; these latter two are generally only applicable to chemo- or biotherapeutics" (Rudmann, 2012: 310). Note that the term "biotherapeutic" refers to any type of treatment that is produced by, or involves, living cells.

Historically, medicines and the first drugs originated from plants and other natural sources. Prior to 1869, patients were limited to natural remedies. Then came the development of the first synthetic drug, chloral hydrate, introduced as a sedative-hypnotic (Jones, 2011). The first pharmaceutical firms, offshoots of the textile and synthetic dye industries of the day, developed so-called "small molecule" drugs for a range of maladies. Drawing on the rich knowledge of organic chemicals, the first analgesics and antipyretics, phenacetin and acetanilide, were simple derivatives of coal-tar. Many of today's most widely recognized medicines, including the first blockbuster drug, aspirin, were simple modifications of historic herbal treatments (Jones, 2011). At the dawn of the twentieth century the first barbiturates entered the pharmacopeia, and the 1970s brought the biologic revolution (Lybecker, 2016).

Biologics

Biologic medicines[2] are at the forefront of medical progress and they have vastly improved the "treatment of conditions such as rheumatoid arthritis, anemia, leukopenia, inflammatory bowel disease, psoriasis, and various forms of cancer. The first biologic, human insulin, was marketed in 1982. Today, biologics are one of the fastest growing segments of the prescription product market" (Biosimilars Resource Center, 2019a). Biological medicines include a wide range of products "such as vaccines, blood and blood components, allergenics, somatic cells, gene therapies, tissues, and recombinant therapeutic proteins" (IGBA, n.d.(a)). In contrast to conventional small molecule drugs, biologics are produced using components of living organisms. These include: human, plant and animal cells, and microorganisms such as bacteria or yeast.

Since biologic medicines are produced with living organisms, biologics are characterized by larger molecules, or mixtures of molecules, and they feature more complex structures than conventional medications. In contrast to traditional small molecule drugs, biologics are not easily characterized, reproduced, or identified. That is, they are difficult to reproduce. By their nature, the production of biologics results in inherent variations, including small differences between lots of the same biologic medicine. These "acceptable within-product variations are normal and expected within the manufacturing process (FDA, n.d.(a)). As a result, the development and manufacturing process for biologic medicines is much more complicated and costly than for small molecule drugs. The Biosimi-

[2] The terms "biologics" and "biologic medicines" are used interchangeably throughout this piece.

lars Resource Center cites a study that found that the average development cost for a biologic is 22 times greater than that of a small molecule drug (Biosimilars Resource Center, 2019a).

Due to both the size and sensitivity of biologics, these medicines are most frequently administered by injection, inhalation, or infusion into a patient's body. While small molecule drugs can be swallowed and enter the human body without being noticed by the immune system, the same is not true of biologics. The large molecules of biologic medicines are always detected, and the human body's immune system must then decide whether to mount an immune response. Specifically, without precise design and administration, the patient's immune system may consider the biologic a foreign substance and take steps to neutralize and eliminate it (Dolinar, 2012; Lybecker, 2016).

Notably, in the United States, a reference product is the FDA-approved single biological product, against which a proposed biosimilar product is compared and evaluated to establish that the product is highly similar and has no clinically meaningful differences.

Small molecule drugs versus biologics

Traditional small molecule medications are smaller in size than biologics and they are made from pure chemical substances. Both of these factors allow for the relatively easy identification and characterization of their structure. Conventional medicines are usually synthesized through a predictable chemical process, allowing for identical reproduction of the medicine (Biosimilars Resource Center, 2019a).

Conventional drugs are typically manufactured through chemical synthesis by combining specific chemical ingredients in an ordered process. These traditional drugs are usually characterized by well-defined chemical structures, such that a finished drug can generally be analyzed to determine all its various components. In contrast to conventional small-molecule drugs, biologics are difficult, and sometimes impossible to characterize through the testing methods available in the laboratory. Moreover, it may be the case that some of the components of a finished biologic are unknown (BIO, 2019).

The manufacturer of a traditional small-molecule drug can change the manufacturing process extensively as long as it can analyze the finished product to establish that it is the same as before the manufacturing change. Conversely, for biologics, "the product is the process." Given that the finished product is impossible to fully characterized in the laboratory, manufacturers have to ensure product consistency, quality, and purity by ensuring that the manufacturing process remains substantially the same over time.

> The living systems used to produce biologics can be sensitive to very minor changes in the manufacturing process. Small process differences can significantly affect the nature of the finished biologic and, most importantly, the way it functions in the body. To ensure that a manufacturing process remains the same over time, biologics manufacturers must tightly control the source and nature of starting materials, and consistently employ hundreds of process controls that assure predictable manufacturing outcomes. Process controls for biologics are established separately for each unique manufacturing process/product and are not applicable to a manufacturing process/product created by another manufacturer. These process controls may also be confidential to the original manufacturer. Therefore, it would be difficult or impossible for a second manufacturer to make the "same" biologic without intimate knowledge of and experience with the innovator's process. (BIO, 2019)

Importantly, the living organisms used in the manufacture of biological medicines are naturally variable. The "microheterogeneity," the inherent degree of minor variability, is thus customarily present in biologic drugs. Moreover, microheterogeneity may also be expressed within and/or between batches of the same biologic (IGBA, n.d.(a)).

Table 2: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Generics	Biosimilars
Product Characteristics	Small molecules Often very stable Easy to fully characterize Mostly without a device	Large, complex molecules Stability requires special handling Hard to characterize Device is often a key differentiator
Production	Chemical Synthesis Simple	Produced in living organisms Highly sensitive to manufacturing changes and environment Complex isolation and purification steps Process affects product
Cost	Relatively low	Comparatively high cost
Development	Very limited clinical trials	Significant R&D Extensive Phase I and III clinical trials

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Table 2: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Generics	Biosimilars
Comparative Clinical Trial	Not required	At least one
Indication Extrapolation	Automatic	Case by case
Regulation	Must be identical to reference product	Must be highly similar to reference product
	Abbreviated approval process in most countries, available for all drugs	Abbreviated approval pathways vary depending on the drug
	"Substitutability" status granted	"Comparability" status
		Approval pathways vary by country, still under development[1]
Marketing	No/Limited detailing to physicians	Required detailing to specialty physicians
	Key role of wholesalers and payers	Pharmacists may not substitute
	Market substitution in pharmacies	Limited price discounts, price sensitivity is product specific
	Significant price discounts	
Interchangeability	Yes	Generally, no
		According to an 2016 EU survey, 26 of the 32 nations (81%) reported that pharmacy-level substitution of biologics was prohibited.
		Interchangeability remains a provincial decision in Canada

Sources: GaBI Journal, 2017; Klein and Wang, 2013; Lybecker, 2014; First Word, 2010; Lybecker, 2016.

1 The approval pathway varies significantly by country and such processes have been adopted over a number of years in different nations. In Europe an abbreviated approval pathway has existed since 2006, while in the United States the legislation was created in 2010 and is still being fine-tuned. In March 2010, Health Canada finalized guidelines for subsequent entry biologics (First Word, 2010, GabI, 2014).

Biosimilars

A biosimilar is a version of a biologic drug that is highly similar to the reference biologic drug; it is available in the Canadian market after the patent on the original product has expired. In Canada, biosimilars were previously termed "Subsequent Entry Biologics" (SEBs) (Health Canada, 2014). The term "biosimilar" describes a subsequent entry version of an approved innovator biologic with demonstrated similarity to a reference biologic drug. According to CADTH (2019), "Biologics are large molecules with complex manufacturing procedures. While the protein sequence is known, the manufacturing process is proprietary. So, it is impossible to exactly duplicate all of its characteristics. In fact, there is even variation between batches of the same reference biologic drug (RBD). This is different from traditional generic drugs, which are small molecules that can be precisely replicated and deemed bioequivalent to the innovator drug." For interested readers, the regulatory requirements for the authorization of biosimilars in Canada may be found in the *Guidance Document* (Health Canada, 2016).

There are many important differences between biosimilars and the generic versions of traditional small-molecule drugs. Table 2 highlights many of these. A biosimilar is a biological product developed to be similar, but not identical, to an existing previously-approved biologic (in a specific jurisdiction), known as the reference product. Given that there is a degree of natural variability in all biological products it is impossible to create an identical copy of a product that comes from living cells. All biologics—including originator reference products—show some batch-to-batch variation (Biosimilars Resource Center, 2019b).

While a biosimilar may feature a different structure than the originator product, the active substances are virtually identical in molecular and biological terms. In principle, there are no clinically meaningful differences in safety or effectiveness between the biosimilar and the originator biologic. Specifically, only minor differences in clinically inactive components are allowable (Biosimilars Resource Center, 2019b). Further, a manufacturer must also establish that its proposed biosimilar version does not clinically differ in safety, purity, and potency (safety and effectiveness) from the reference product. This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies (FDA, n.d.(a)).

For readers interested in a more detailed, in-depth description of biosimilars, the Research Advocacy Network (n.d.) has produced an excellent introduction to biosimilar medicines that describes the basics, the science, the regulatory process, and a discussion of the economics of biosimilars.

Generic drugs versus biosimilars

Generic versions of conventional small molecule drugs are chemically identical to their innovator counterpart. These exact copies have the same active ingredient, strength, dosage form, route of administration, safety profile, performance characteristics, and intended use as the innovator (reference) drug. In addition, the generic drug must be bioequivalent. Bioequivalence is established through relatively simple analyses such as blood level testing, without the need for human clinical trials. As a result, generic versions of reference drugs are chemically identical and act the same way in the body as the innovator drug. In approving a generic drug, the generic version is determined to be "therapeutically equivalent" to the innovator drug and is interchangeable with it (BIO, 2019; Biosimilars Resource Center, 2019b).

In contrast, the determination of interchangeability is much more complicated for biologics and biosimilars. In the US, the FDA has stated that it has not determined how interchangeability can be established for complex proteins. Historically, interchangeability has only been permitted by the FDA when two products have been determined to be "therapeutic equivalents." Given that biosimilars are produced through a new manufacturing process, beginning with new starting materials, they are different from and not therapeutically equivalent to that of the innovator (BIO, 2019). Accordingly, it is only through clinical trials that regulatory authorities can establish whether there are differences that affect the safety and effectiveness of biosimilars. In Canada, regulatory authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug. Health Canada states that the authority to declare two products interchangeable rests with each province and territory according to their own rules and regulations. The qualifications of these entities shed doubt on whether they are best qualified to make these decisions. In the EU, interchangeability equates to "changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of, the prescriber. Thus, the European type of interchangeability is not a legal but a scientific and medical term" (Brennan, 2017).

History

While biologics are at the forefront of medical progress, they have a long history dating back to the US Biologics Control Act of 1902. The law was the first aimed at ensuring the safety of vaccines, one of the earliest biologics. The motivation marks a sad moment in history. The US Congress passed the legislation only after a contaminated batch of diphtheria shots resulted in the deaths of 13 children. Tragically, the horse from which the diphtheria antitoxin was extracted had contracted tetanus and that disease was then passed on to the inoculated children (Haydon, 2017).

In the years since, scientific improvements have advanced the techniques for manufacturing biologic drugs. Notably, the recombinant DNA revolution of the 1970s provided innovators with alternative mechanisms for extracting biologics such that animal production is no longer essential. "The gene that codes for human insulin, for example, can be pasted into a microbe which will happily churn out the drug in bulk. After a multi-million-dollar purification process, the injectable insulin that results is indistinguishable from the version a healthy human body would produce. This is how some forms of insulin are made today" (Haydon, 2017). The history of important achievements in the development of biologic medicines and biosimilars dates back to the early 1980s when the first biological medicinal products produced by DNA recombinant techniques were approved. In 1986, a monoclonal antibody received first US FDA approval and in 1998 the first biological medicine for rheumatoid arthritis was introduced. Then, in 2006, Europe approved its first biosimilar medicine. By 2014, over 245 biologic medicines had been approved in the EU and US, representing 166 different active substances (IGBA, n.d.(a)).

It is worth noting that Europe is a pioneer in biologic medicines and biosimilar production. In 2006, the first worldwide biosimilar medicine, somatropin, was approved in the European Union. (The drug was approved by the EMA in 2006 and marketed in Europe under the name Omnitropin.) Then, between 2006 and 2013, patient access in Europe increased significantly, driven by the availability of biosimilars as well as expanded indications. In 2013, the first biosimilar monoclonal antibody was approved in the EU, infliximab (two biosimilar versions are named Inflectra and Remsima). Currently, EU-approved biosimilar medicines are available in more than 60 nations and in 2016, European uptake accounted for 87 percent of the global biosimilar medicines market (IGBA, n.d.(e)).

Development and Manufacturing

Biologics cost more to develop and manufacture than do small molecule drugs. In addition, they also require more time to bring to market—an average of 10 to 15 years as compared to 7 to 10 years for a small molecule drug (Cancer Action Network, 2018). In addition, while a typical manufacturing process for a small molecule drug might require 40 to 50 critical tests, the process for a biologic medicine may include 250 or more (Morrow and Felcone, 2004). As characterized by Morrow and Felcone (2004), table 3 identifies and defines many of the categories of biologics.

Biologic medicines are produced in living cells, which means that the manufacturing processes are highly complex. The production of biologic medicines involves five stages: (1) Cloning DNA into host cells, (2) Fermentation, (3) Harvesting, (4) Purification, and (5) Formulation. Embodied in this five-stage process are thousands of steps, each of which is intricate, highly delicate, and requires precise technique and execution. Given that many steps are particular to an individual medicine, they may require robust quality control systems, expertise, and extensive monitoring (Amgen, 2014). As such, biologics are more difficult to chemically characterize[3] and to manufacture than small molecule drugs, such that even minor differences in production processes or cell lines can generate variations in the resulting protein. Accordingly, an individual patient's responses may significantly depend on how the biologic is produced. Consequently, quality control is even more critical and production complications are potentially more catastrophic than in the production of small molecule drugs. This possibility is starkly illustrated by several recent incidents such as the 500 cases of fungal meningitis linked to contaminated injectable corticosteroids formulated by the New England Compounding Center in October 2012, and the 150 deaths resulting from tainted Chinese heparin in 2008 (Greenemeier, 2008). Importantly, immunogenicity problems may result even from minute changes made by the pioneering company under strictly

[3] "The goal of chemical and material characterization is to identify and quantify the chemical constituents and physical mechanical properties to help establish biological safety" (Albert, 2012).

Table 3: Selected Categories of Biologic Agent Structure

Hormone (Growth Hormone, Insulin, Parathyroid Hormone)	A substance, usually a peptide or steroid, produced by one tissue and conveyed by the bloodstream to another to effect physiological activity, such as growth or metabolism.
Interferons	Proteins that are normally produced by cells in response to viral infection and other stimuli.
Interleukins	A large group of cytokine proteins. Most are involved in directing other immune cells to divide and differentiate.
Growth Factor	A substance such as a vitamin B12 or an interleukin that promotes growth, especially cellular growth.
Monoclonal antibodies (MAbs)	A single species of immunoglobulin molecules produced by culturing a single clone of a hybridoma cell. MAbs recognize only one chemical structure, i.e., they are directed against a single epitope of the antigenic substance used to raise the antibody.
Polypeptides	Peptides containing ten or more amino acids. Typically, a peptide consists of fewer than 50 amino acids, while a protein has more than 50 amino acids.
Proteins	Naturally occurring and synthetic polypeptides having molecular weights greater than about 10,000 (the limit is not precise).
Vaccine	An agent containing antigens produced from killed, attenuated or live pathogenic microorganisms, synthetic peptides, or by recombinant organisms. Used for stimulating the immune system of the recipient to produce specific antibodies providing active immunity and/or passive immunity in the progeny.

Source: Morrow and Felcone (2004)

controlled conditions. Consider the case of EPREX[4] as described by the Biotechnology Industry Organization (BIO):

> Immunogenicity is an important concern regarding the safety of biologics. This occurs when our bodies treat a protein as if it is a foreign substance and try to attack the protein with antibodies. Unlike chemical drugs, all biologics have the potential to stimulate antibody production in patients and such responses are highly unpredictable. Sometimes the antibodies produced in response to a biologic have no effect. Other times they bind and inactivate the biologic, causing disease progression. In still other cases, they can bind to and inactivate a patient's naturally occurring protein, which means that the patient may be left with no options other than regular blood transfusions.
>
> One example of immunogenicity occurred a few years ago when, at the request of the European Health Authorities, Johnson & Johnson made a change in the manufacturing process for its EPREX product––a product that had been marketed for a decade with no evidence of immunogenicity problems. The change caused a serious adverse reaction in a small number of patients. These patients lost their ability to make red blood cells because they produced an antibody (triggered by the EPREX) that inactivated both the administered protein (EPREX) and the body's natural protein that is essential for red blood cell production. Johnson & Johnson eventually was able to determine the cause of this adverse reaction and correct it, but only after a very lengthy and expensive investigation.
>
> The EPREX case shows that one protein can be different from another in ways that cannot be detected in the laboratory but are seen only by the body's exquisitely sensitive immune system. If one change to a well-established complex manufacturing process, made by the manufacturer who has intimate knowledge of the process, can cause a problem with immunogenicity, surely the risk is even greater with an entirely new manufacturer and process––as will be the case with follow-on biologics. (BIO, 2019)

[4] EPREX® is synthetic erythropoietin (epoetin alfa) which increases the production of red blood cells and reduces the need for transfusions of red blood cells. It is produced naturally in the body, primarily by the kidneys. Without sufficient epoetin alfa, severe anemia (lack of oxygen reaching the different parts of the body) can occur. EPREX is used to treat patients with chronic kidney disease (CKD) because their kidneys are unable to produce enough natural erythropoietin on their own. In addition, it is used to treat cancer patients who develop anemia because of chemotherapy treatment.

Given that a tiny change in the manufacturing process, raw materials, temperature, pH, or cell line may result in a marked alteration in the medicine's quality, efficacy, or safety, the interchangeability and substitutability of these products must be approached with extreme caution. The importance of these elements is all the more acute given the complexity of biologic medicines. Biomanufacturing is the production of biological products from living cells. While small molecule drugs can be synthesized chemically, biologics require living cells. Biologic drugs have molecules that are characterized by large size, lack of uniformity, and weak chemical bonds. The molecules that comprise a biologic drug are not uniform, and each molecule typically has a multitude of atoms. While conventional medicines contain a small number of atoms (there are 21 atoms in aspirin: nine carbons, eight hydrogens, and four oxygens), biologics generally contain tens of thousands of atoms. In addition, the molecules are held together by relatively weak chemical bonds and the molecules can degrade if they are exposed to rapid temperature changes and other factors such as shaking. Given that the molecules that make up biologics are so sensitive, specific steps must be followed in their manufacture and packaging. Even minor differences in the manufacturing, packaging, storage and administration of a biologic medicine can affect a drug's ability to work and result in adverse effects in patients (de Falla, 2017; Haydon, 2017; and Burke, 2018).

To date, most modern biologics are assembled inside vats or bioreactors that house genetically engineered microbes or mammalian cell cultures. In addition, efforts are under way to manufacture them in plants. "Biologic drugs can be whole cells, alive or dead. They can be the biomolecules produced by cells, like antibodies, which are normally secreted by our immune system's B cells. Or they can be some of the internal components of cells, like enzymes" (Haydon, 2017).

Burke (2018) provides an excellent description of the biomanufacturing process:

> Biomanufacturing involves engineering a cell to produce a specific protein. Using well-established techniques, scientists transfer a gene encoding the desired protein into a "production cell." The two most commonly used production cells are E. coli bacterial cells and Chinese hamster ovary cells, or CHO cells. Once a manufacturer successfully manipulates a cell to produce said protein, the cells multiply. Scientists call these genetically identical cells the production cell line. Step two is for the manufacturer to establish a master cell bank that supplies genetically identical cells for future products. Companies create cell banks by transferring the production cell line to a bioreactor. Though they may sound scary,

> bioreactors are simply vessels filled with a growth medium — a "broth" with the required nutrients brewing in optimal conditions of temperature, pH, and oxygen concentration for cell growth. The cells are left to simmer, or multiply for a few generations, creating hundreds of millions of identical copies. The manufacturer collects this slough and portions them into small vials. Each of the several hundred receptacles contains about a million… cells. The vials are then frozen with liquid nitrogen, cooling them to -196 degrees Celsius. The deep freeze stops cell growth; in other words, if some future scientist thawed one of the vials in twenty years, she or he would find the cells inside exactly as they were at storage—barring apocalypse or someone tripping over the power strip. This stable longevity is key, as product consistency over the lifetime of the product is critical to drug safety. Manufacturers typically divide the master cell bank for storage in three separate locations so that disaster in one place doesn't wipe out this important resource. In each location that a product is manufactured, a manufacturer creates a working cell bank by thawing one vial from the master cell bank and "expanding it," or allowing it to multiply for a few generations – and then freezing several hundred vials for storage. Each new biomanufacturing campaign starts by thawing a vial of cells from the working cell bank.

Insulin was the first biologic drug and it was produced using E. coli cells. Researchers quickly recognized the limitations of producing drugs in bacterial cells. Notably, very complex proteins, such as monoclonal antibodies and certain enzymes, present two main obstacles. Burke (2018) notes that "bacterial cells are unable to correctly fold these complex proteins, nor are they able to confer required post-translational modifications – chemical and physical changes made to a protein by cellular enzymes after the protein is produced." At the time that scientists realized that other manufacturing methods were needed, Chinese hamster ovary cells (CHO cells) were already being used in many experiments. They created a convenient platform for the production of biologics and 30 years of data have established their safety. Accordingly, the US FDA granted them "generally-regarded-as-safe" (GRAS) status for therapeutic protein production. Given this, biologic manufacturers can use CHO cells to produce their products without first demonstrating their safety (Burke, 2018).

Quality control and good manufacturing processes are critical for all medicines, and even more so for biologics. Accordingly, the growing share of imported medicines and offshore manufacturing and the quality issues associated with them are very troubling. Consider that 62.3 percent of the Canadian market is supplied by foreign imports (Lybecker, 2016) and

that India now comprises the second-largest exporter to Canada, accounting for close to one of every 20 finished prescription products (Blackwell, 2015). As such, safety lapses are tremendously worrisome: In 2015, Health Canada halted the importation of 16 medicines and other drug products from Indian manufacturers due to growing health and safety concerns (Blackwell, 2015) and in August of 2015, the EU instructed its 28 member nations to halt sales of 700 Indian-made generic drugs amid concerns about the integrity of clinical trials (Kazmin and Ward, 2015). Given that these issues arise in the relatively straightforward production of small molecule drugs, the dangers surrounding the production of biologics could be much worse.

Regulatory Pathways for Biosimilars

The first body to develop a comprehensive framework for the approval of biosimilars was the European Medicines Agency (EMA). This was done in 2006 and since that time, frameworks for the approval of biosimilars have been developed by numerous other countries, including Australia, Japan, and Latin America.

In the United States, the regulatory framework for the approval of biosimilars originated in 2010 with the Biologics Price Competition and Innovation Act (BCPIA), a provision included in the Patient Protection and Affordable Care Act (Affordable Care Act). The abbreviated licensure (approval) pathway is available for biosimilar products that have the same mechanism of action, route of administration, dosage form, and strength as the original reference product. Importantly, the biosimilar may only be approved for the indications and conditions of use approved for the reference product (Biosimilars Resource Center, 2019c).

Biologics are structurally complex and more difficult to replicate than small molecule pharmaceuticals. In order to satisfy Health Canada, a biosimilar must demonstrate that it is "highly similar" to the reference product, and that there are no "clinically meaningful differences in terms of safety and efficacy between them." Health Canada uses a "totality of the evidence" approach to demonstrate biosimilarity to the reference product and evaluate applications for biosimilar products. While the process is difficult, it is important to recognize that it is nonetheless less burdensome than for original biologics (Scott and Wang, 2018). The various types of data used to establish biosimilarity include:

- Analytic studies demonstrating that the structure and function of the biosimilar are "highly similar" to the reference product.
- Animal studies, including assessment of toxicity.
- A clinical study or studies, including assessment of immunogenicity (whether the biosimilar produces an unwanted immune response) and pharmacokinetics or pharmacodynamics (Biosimilars Resource Center, 2019c).

Table 4: Types of Data to Support Biosimilarity

Highly Similar	
Analytical Studies	Assess an array of quality characteristics using state-of-the-art technologies and multiple different tests for the same characteristic to determine if the proposed biosimilar is highly similar to the reference product Identify differences in quality characteristics, if any, between the reference product and proposed biosimilar (Examples of critical quality characteristics include structure and bioactivity) Thoroughly evaluate the potential impact of any differences observed
Assessment of Toxicity	
Animal Studies	Support safety decision prior to human exposure to the proposed biosimilar May provide additional support for demonstrating biosimilarity, but are not always needed
No Clinically Meaningful Differences	
Human PK and PD Studies	Compare the pharmacokinetic (exposure) and, as applicable, pharmacodynamic (response) profiles of the reference product and proposed biosimilar to support a conclusion of similar efficacy and safety Generally considered the most sensitive data element to support a demonstration of no clinically meaningful differences.
Immunogenicity Assessment	Compare incidence and severity of immune responses generated with the reference product and proposed biosimilar Generally included as part of all clinical studies
Additional Clinical Studies	Conducted only when residual uncertainties remain about the demonstration of no clinically meaningful differences after conducting the above-named studies Different from the role of Phase 3 efficacy and safety trials conducted to support traditional drug development
Experience with Reference Product	

Source: US FDA, n.d.(b)

In contrast to the generic versions of conventional small molecule drugs, biosimilars are costlier and more difficult to produce. While a generic version can be developed and brought to market in approximately two years for a cost of $1 to $10 million, a biosimilar may require 5 to 10 years to develop and an investment of US$100 million to $250 million. This distinction is only heightened by the complex patent landscape of biologics (Einstein, 2019).

The significant cost of developing a biosimilar results in part from the regulatory approval process's emphasis on biological and physiochemical characteristics. While the pathway for approving reference biologics emphasizes large clinical studies that establish safety and efficacy, the pathway for approving biosimilars places greater emphasis on the biological and physicochemical characterizations of the biosimilar molecule, because the safety and efficacy data for the reference product are readily available (Biosimilars Resource Center, 2019d).

Studies to establish biosimilarity should be conducted in a stepwise manner: "Ideally, extensive initial analytic testing demonstrates minimal or no qualitative or quantitative differences in the structure and function of the proposed biosimilar and the reference product" (Biosimilars Resource Center, 2019d).

In the end, a review of the totality of the evidence should establish that a biosimilar is essentially the same drug as the originator reference product. Moreover, it should be established that it will work the same way as the originator reference product for its approved indications.

The process for approving a biosimilar may be broken down into several distinct steps. According to Einstein (2019), the six-step process for approving a biosimilar is:

1. **Reverse engineering.** The original biologic is analyzed with methods such as mass spectrometry to reveal its amino-acid sequence, protein structure, and any chemical modifications. These profiles will be compared with those of prospective biosimilars.

2. **Cell-culture conditions.** Even when following the same genetic instructions, different cell lines can produce variants of a particular protein. Biosimilar developers must therefore identify an appropriate cellular factory and optimize those cells' growth conditions to ensure that their product closely resembles the original biologic.

3. **Testing the function.** Various assays are used to test how well a prospective biosimilar binds to its biological target and to confirm that the drug replicates the effect and specificity of the original biologic.

4. **Finding the formulation.** If a biologic is not properly prepared or mixed, it can misfold, degrade, or aggregate. Consequently, biosimilar developers must identify manufacturing methods that result in a stable, reliable product.

5. **Clinical confirmation.** Testing a biosimilar in people is faster than evaluating a biologic. Typically, only a phase I trial to show that the drug is safe and a phase III trial to show that it has an efficacy similar to that of the original are needed.[5]

6. **Regulatory review.** On the basis of the clinical data, a regulatory authority decides whether the a biosimilar is sufficiently similar to the original biologic. Further testing in people might be required (Einstein, 2019).

[5] In essence, the savings for biosimilars result from the ability to skip Phase II testing.

Naming

As the Mark Twain quote indicated earlier, the right words are very important. So is the right name. In the context of biosimilars, the issue is whether they should have the same International Proprietary Name (INN) as the innovators' biologics. Internationally, the global INN system is overseen by the World Health Organization. Since their recommendations are not mandatory, some innovator firms are increasingly worried about regulators in different countries being free to pursue different approaches for identifying biosimilars (Silverman, 2014).

Specifically, at issue is whether the names will allow patients and physicians to distinguish innovator biologics from biosimilars. "Brand name drug makers and biotechnology companies want biosimilars to have unique, non-proprietary, or generic names to distinguish the medicines from the original biologics, which differ from other drugs because they are created by biological processes, rather than being chemically synthesized. In the view of the brand name drug makers, distinct names would lessen confusion in the marketplace and, therefore, ensure patient safety. But generic drug makers disagree and believe that creating a new standard for biosimilars would, in fact, create confusion" (Silverman, 2014).

For its part, Health Canada has determined that biologics drugs will be delineated by a unique brand name, a non-proprietary name, and their unique drug identification number (DIN). Health Canada explained that "'Since a biosimilar and its reference biologic drug are not identical and are manufactured by independent processes, newly identified safety issues that affect the reference biologic drug may or may not also affect the biosimilar and vice-versa.' At the same time, Canada's federal institute rejected the possibility of adding a product-specific suffix, which leaves the US Food and Drug Administration (FDA) as the only regulatory body requiring such an identifier" (Hargreaves, 2019).[6]

[6] "In 2017, the US Food and Drug Administration (FDA) published guidance to include a random four-letter suffix to the international nonproprietary names (INN) of all biological products. The ruling essentially distinguished a biosimilar from its reference product, so Amgen's reference product Neupogen, for example, is known as 'filgrastim-jcwp,' while Sandoz's biosimilar version Zarxio – the first biosimilar approved and launched in the US – is known as 'filgrastim-sndz'" (Stanton, 2019).

Interchangeability, Switching, and Substitution

Traditional medicines—small-molecule drugs—are easily identified and replicated since they are composed of known chemical compounds. In contrast, as discussed earlier, biologic medicines are produced by genetically modified, living cells that secrete proteins. These cells are finicky and unpredictable, such that copies are called "biosimilars," rather than generics. The highly sensitive manufacturing processes result in copies that are not interchangeable, and studies suggest that patients who are well established on the innovator biologic cannot easily be switched to a biosimilar. Biologic medicines have many more places for variation. As a consequence, even slight irregularities may potentially alter how patients respond (Weaver, Whalen, and Rockoff, 2013; and Lepage, 2015).

Slight differences in biologic medicines may result in reduced efficiency or induce immunogenic responses. These complications may even occur when the original manufacturer "makes slight known changes (evolution) or unknown changes (drift) to its own production process, which can then yield a product that diverges from its predecessor" (Sarpatwari, Avorn, and Kesselheim, 2015: 2). The potential for differences is even more acute across different manufacturers, such that no two products are identical due to different amino acid sequence, impurities, and 3D structure. As a result, regulatory authorities require far more extensive testing for biosimilars than for generic drug products. Moreover, "because biosimilar manufacturers don't have access to any information regarding the processes by which the original drug is manufactured—that information is a trade secret—it is almost a foregone conclusion that the biosimilar product will be different from the original as well" (Gaffney, 2014: 1).

> According to the BPCIA, for a biosimilar product to be designated as interchangeable, the manufacturer must provide additional evidence that the biosimilar is expected to produce the same clinical result as the reference product in any given patient. In addition, the manufacturer must show that patients may use both products safely and without any loss in efficacy. Specifically, if the biosimilar is administered more than once to a patient, the risk (in terms

> of safety or reduced effectiveness) associated with alternating or switching between the biosimilar and the reference product cannot be greater than the risk of using the reference product continuously. None of the biosimilar products approved so far in the United States have been designated as interchangeable. (Biosimilars Resource Center, 2019e)

Although biosimilars are never identical to the innovator biologic, biosimilars are required to have the same quality and therapeutic effects as the reference product. In clinical studies, biosimilars are often simply required to show that they are "non-inferior" to the reference biologic in quality and safety. The choice of an appropriate "non-inferiority" margin is controversial, as was demonstrated in the case of the NOR-SWITCH study. The study showed comparable results overall between the biological drug (infliximab) and the biosimilar (CT-P13) for disease worsening and safety following non-medical substitution, although it was not designed to demonstrate non-inferiority in each of the six diagnostic groups examined. Their subjective choice of a (higher than usual) 15 percent margin of non-inferiority was also contentious. In fact, for Crohn's disease (32 percent of the study sample), the clinical results showed a difference of 14.3 percent in favour of the biological drug compared to the biosimilar (Jørgensen et al., 2017).[7]

Notably, even the minor differences between the two could lead to unexpected adverse events for patients. In the case of such an event, regulators must be able to distinguish the biosimilar from the biologic in order to establish whether the patient's adverse event was caused by a biologic, a biosimilar, or both. To date, that determination is difficult because an increasing number of biologics and biosimilars share the same non-proprietary name (AAPS, 2019).

The differences between biologics and biosimilars have led to a significant debate over substitution and the development of a system to identify each type of medicine. The specific point of contention is whether a system of International Nonproprietary Names (INN) should be used to identify pharmaceutical substances or active pharmaceutical ingredients. The goal of an INN system is to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. However, there are questions about whether different INNs would inhibit substitution and thus reduce the cost savings generated by biosimi-

[7] The author is grateful to an anonymous reviewer for the information about the NOR-SWITCH study. A critical assessment of the trial may be found at: https://care-education.squarespace.com/gastro-publications-blog/2017/1/26/care-perspectives-on-the-nor-switch-trial.

lar copies. "'If pharmacists or physicians see a different name, they may wonder whether the product is really the same and if they have to look up dosing or regimens,' says Mark McCamish, who heads global biopharmaceutical development at Sandoz, the generic drug maker owned by Novartis" (Silverman, 2014).

> This explains why industry squabbling was the focus of a WHO meeting in Geneva in October 2013, where the agency faced increased pressure to establish an INN system for biosimilars. Generic drug makers urged the agency not to memorialize the use of different names for these medicines, while also avoiding the use of prefixes or suffixes, a tactic sometimes used in Europe to distinguish rival brand name biologics. In Australia, for instance, the government issued a draft proposal that would require biosimilar names to be followed by a suffix, so that the follow-on medicine is seen as a unique version of the original drug. In Japan, a different approach is being taken where the INN is followed by letters for both a biosimilar and a brand name biologic" (Silverman, 2014).

Early in 2019, Health Canada decided that it would not use the controversial four-letter suffixes adopted by the US Food and Drug Administration (FDA) for naming biosimilars and biologics. Health Canada cited the potential for confusion as a concern. Health Canada contends there is already sufficient information to distinguish a biologic from a biosimilar, specifically the unique Drug Identification Number (DIN) assigned to all drugs, including biologic medicines and biosimilars. The DIN includes information about the drug's brand name, manufacturer, active ingredients, strength, dosage form, and route of administration. Arguably, in its totality, this information should allow for the correct identification of a biologic or a biosimilar (AAPS, 2019).

In switching to a biosimilar, Health Canada historically explicitly recommended that the switching decision be made by the treating physician in consultation with the patient. This no longer appears to be the case. In August 2019, Health Canada updated its information about biosimilars and biologics, subtly modifying the language to provide the impression that any substitution may be considered safe (Health Canada, 2019b). Health Canada considers "a well-controlled switch from a reference biologic drug to a biosimilar in an approved indication to be acceptable and recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar, or between any biologics, be made by the treating physician in consultation with the patient and take into account available clinical evidence and any policies of the relevant jurisdiction" (Pfizer Canada, 2020).

While the issue is beyond the scope of this study, it is essential to consider the global clinical and economic implications of mandatory substitution, switching for non-medical reasons. This particular issue is central to the current public policy debate in Canada, as reflected in the BC government's biosimilar initiative. Such substitution is not without risk. Minutolo et al. (2017) found that "in stable dialysis patients, switching from ESA originators to biosimilars requires 40% higher doses to maintain anemia control." Recent systematic reviews of the economic impact of mandatory substitution may be found in Liu et al. (2019), McKinnon et al. (2018), and Glintborg et al. (2019). A review of recent studies reveals that cost estimation and simulation studies demonstrated the cost reduction associated with non-medical substitution. However, variation across studies was substantial because of heterogeneity in study designs and assumptions.

Market Conditions and Competition

The market

Biologic medicines are developed with an understanding of the mechanisms of diseases, such that the biologics can target and modify the underlying causes of those diseases. Those biologics may alter the course of the disease, rather than merely treating the symptoms (Amgen, 2014). In the near future, "a further generation of biologic drugs will start to deliver cures by using viruses to deliver 'gene therapy'— the replacement of a faulty gene in a patient's body cells with the correct version" (The Economist, 2014).

Biologic medicines were virtually nonexistent a decade ago, but sales rose to US $157 billion in 2011 (Weaver, Whalen, and Rockoff, 2013). Moreover, in 2011, global spending on biologic medicines increased by 7.0 percent, compared to a mere 1.2 percent growth in the small molecule pharmaceutical market (Richardson, 2013). Monoclonal antibodies (MAB) and human insulin are the principal drivers of growth in this sector. According to IMS Health, global sales of biosimilars could reach $25 billion (US) by 2020 (Silverman, 2014). In 2016, biologics (including biosimilars) made up 25 percent of the total pharmaceutical market, approximately US$232 billion (Haydon, 2017). Moreover, it is anticipated that biological medicines will account for 30 percent of new drug products launched between 2016 and 2020 (IGBA, n.d.(b)) and accounted for close to one-quarter of global drug spending in 2015 (Einsenstein, 2019). Figure 1 shows the market share specifics. These fractions are on track to grow in the years to come.

While currently a growing source of revenue, the market exclusivity enjoyed by many of these products will erode as patents expire and competing products enter the market. In 2016, biologics with sales totaling US$60 billion [lost] patent protection in the US market (Silverman, 2015). Beyond patent expiry, these revenues are also threatened by increasing scrutiny by government health agencies and other payers. As *The Economist* reported (2014), the governments of Italy and France have taken note that Avastin, a biologic developed for cancer, also treats macular degen-

Figure 1a: Worldwide Drug Sales (US$776 billion) in 2015

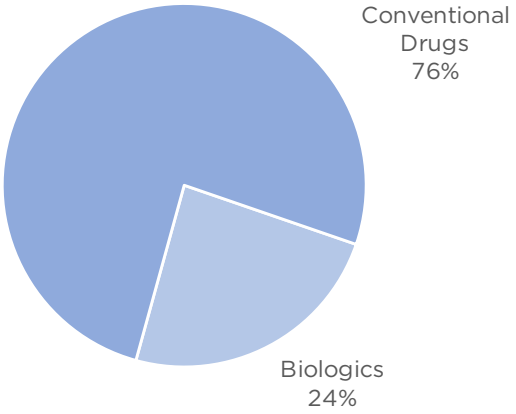
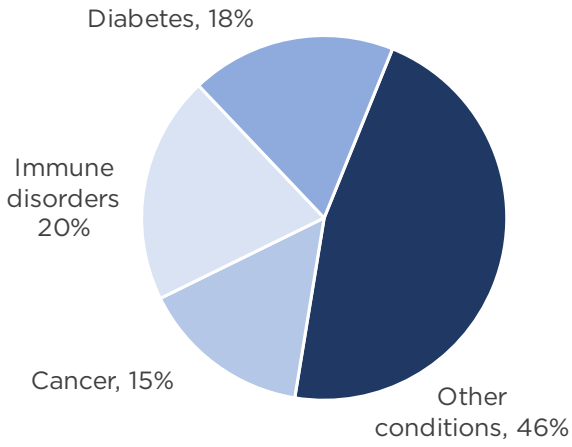


Figure 1b: Global Spending on Biologics by Condition in 2015



Source: Eisenstein, 2019.

eration and that Avastin is significantly less expensive than Lucentis, the biologic currently used to treat macular degeneration. The governments of France and Italy have approved Avastin for the treatment of the condition and according to one French legislator, the substitution will save France's health service $273 million a year compared with using Lucentis (The Economist, 2014). A similar situation exists in Canada where the prevalence of off-label use is estimated at 11.0 percent; and of the off-label prescriptions, 79.0 percent lacked strong scientific evidence (Eguale et al., 2012). Pharmacoepidemiologist Dr. Nigel Rawson examined the Canadian Agency for Drugs and Technologies in Health (CADTH) health technology assessment (HTA) of a selection of drugs for the treatment of vision loss, concluding that the recommended reimbursement by CADTH for "off-label" use of Avastin was done merely to accommodate provincial government cost-containment objectives, despite the fact that the drug does not have Health Canada safety approval for the indication and despite the potential health risks to patients (Rawson, 2015). This adds to the increasing evidence that cost-containment is a critical factor in drug selection and approval. Such off-label use essentially undermines the guarantees of the patent system and the intellectual property rights of the innovators.

The complexity of biologic medicines come at a high price. Brineura is the most expensive medicine ever made. It is a biweekly enzyme replace-

ment therapy produced by BioMarin Pharmaceutical which delays the loss of walking in individuals with a rare genetic disorder. The drug is priced at $27,000 per injection, which comes to more than $700,000 for a full year's treatment (Haydon, 2017).

In the market for small-molecule pharmaceuticals, economic research has established that competition drives prices to the near perfectly competitive level. Bresnahan and Reiss (1991) find that this occurs with only three entrants. In contrast, according to a 2007 study by Grabowski, Ridley, and Schulman, biosimilars will have high fixed costs from clinical testing and manufacturing such that there will be less competition – fewer entrants – than would be expected for generic pharmaceuticals. This will also result in more modest cost savings through biosimilar entry. Despite these industry dynamics, the accumulated savings across biologics is estimated to be significant.

However, it is essential to recognize that competition will come from other biologic drugs as well as biosimilars. DiMasi and Chakravarty (2016) found that "the large molecule first-in-class compounds faced competition in the class somewhat sooner [than small molecules]. For the overall period, the mean time to a second entrant approval was 14% lower for large molecules (3.6 vs. 4.2 years). The median time to a second entrant approval was 48% lower for large molecules (1.5 vs. 2.9 years)." In related work, Roediger et al. (2019) examined the effects of competition between on-patent medicines and found that competition brought more and better treatment options for patients along with lower costs for payers (e.g., new biologics for the treatment of Hepatitis C).

The largest pharmacy benefits manager in the US, Express Scripts, estimates that nationwide savings of roughly US$250 billion could be achieved between 2014 and 2024 if biosimilar versions of just 11 widely used biologics were to suddenly become available. In like manner, across eight European Union countries (Germany, France, Italy, the United Kingdom, Spain, Sweden, Poland, and Romania) the cumulative savings from biosimilars would equate to between US$16 billion and US$45 billion between 2007 and 2020, according to data from the IGES Institut, a German health care consulting firm (Silverman, 2014). While the savings seem promising, the approval and availability of these biosimilars are constrained by regulatory and intellectual property considerations.

> In many countries generic manufacturers can secure approval to market their generic versions of biologics without clinical trials if they can show that their generics are "bio-equivalent" to an approved drug. Under data exclusivity protection, however, data submitted to a regulatory agency to demonstrate the safety and effectiveness of a new drug by the drug's original developer cannot

> be used by generic manufacturers when seeking approval of their competing products. This requires generic manufacturers to either conduct their own studies, typically an expensive proposition, or to wait until the exclusivity period is over, thus delaying the introduction of the generally cheaper generic version to the market. (McCarthy, 2015)

Canada approved the first biosimilar in 2014: Inflectra for the biologic medication Remicade (infliximab), which is used to treat rheumatoid arthritis and psoriasis. The biosimilar was priced at a 30 percent discount relative to Remicade. This approval opened the biologic market to additional competition and may have contributed to the announcement of several significant product listing agreements between Janssen and some major private payers to reduce the price of Remicade (Lepage, 2015).

Cost savings

As noted earlier, biosimilar medicine development costs from US$100 million to US$300 million per drug and requires up to eight years (IGBA, n.d.(d)). This is a significant commitment of time and financial resources and results in a drug that is quite expensive. However, the largest breakthroughs are initially made by innovative pharmaceutical companies that bring their biologic products to market. This is also the cutting edge of medicine and estimates place the cost at 10 to 15 times that of a biosimilar.

> Following the maturation of recombinant DNA technology in the 1970s, biologics have been emerging as a prominent class of pharmaceuticals. To illustrate, seven out of the 10 best-selling pharmaceuticals in 2018 were biologics, including Humira, Opdivo, Keytruda, Enbrel, Herceptin, Avastin and Rituxan. The world's best-selling pharmaceutical, Humira, which is prescribed for a variety of autoimmune diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and juvenile idiopathic arthritis, brought in nearly US$20 billion in worldwide sales last year.… In a few cases of biologics indicated for the treatment of rare diseases such as neuronal ceroid lipofuscinosis type II or Batten disease and spinal muscular atrophy the price comes closer to a million dollars per treatment year. As a result, although biologics account for only about 1 to 2% of prescriptions written in the United States, they are responsible for more than 30% of the spending on pharmaceuticals overall and their "share" in pharmaceutical spending only continues to grow. (Heled, 2019)

In the case of small molecule drugs, at the moment of patent expiry, generic entry and increased competition drive down the price. Numerous studies have shown that the introduction of generic versions of a small molecule pharmaceutical can reduce prices by 90 percent relative to the branded version, which has saved US consumers more than $1.5 trillion over the past decade. Similar savings cannot be expected from biosimilars. Unlike generic versions of traditional small molecule drugs, biosimilars are not identical to the originator biologic. Given that they are only similar to the originator biologics, the biosimilars will require their own lengthy and expensive clinical trials in order to ensure that they are safe and effective (Haydon, 2017). In contrast, Silverman (2014) notes that biosimilars are expected to reduce prices by a more modest 20 to 30 percent. This echoes the estimates provided by CADTH (2014), which noted that biosimilars currently marketed in the European Union are priced 20 to 30 percent lower than their respective reference biologic products. Meanwhile, the Federal Trade Commission estimates that biosimilars will only provide a 10 to 30 percent price reduction in the United States (Haydon, 2017) and the Research Advocacy Network (n.d.) suggests a price 20 to 30 percent less in the US than the originator biologic.

Table 5 provides the estimates from numerous academic studies of the savings available to the United States from the use of subsequent entry biologics. As the table shows, current opinions on the estimated savings vary widely. According to the US FDA, "among generic small-molecule drugs, prices reach the maximum savings level only when 10 or more competitors are on the market – an unlikely occurrence for many biologics. In the European Union, where 22 follow-on biologics are available, the median price savings for biosimilar epoetin alfa is just 35%" (Sarpatwari, Avorn, and Kesselheim, 2015: 2). According to Howell (2012), the discount will average even less. This study notes that within Europe, subsequent entry biologics offer just a 10 percent discount from the pioneer product. While the potential cost savings from subsequent entry biologics is frequently cited as a reason for lessening the extent of intellectual property protection, it is unclear how significant these savings will be and how easily and quickly they will be realized.

Despite the more modest cost savings, the numbers still add up to a significant amount. The RAND Corporation estimates US savings of $44 billion over the coming decade (The Economist, 2014), while Express Scripts calculates a potential saving of $250 billion in the next decade (Lybecker, 2016).[8] Moreover, these findings are arguably economically

[8] The differences in these two calculations reflect the different assumptions made in the studies: extent of the price discount, degree of substitutability, and uptake, among others.

Table 5: Select U.S. Biosimilar Cost Savings Estimates

Study	Approach	Scope	Time Frame	Price Reduction	Savings
Grabowski et al., 2007 as applied in Goodman et al., 2009 (base case)	Economic model	6 major categories of biologics, top 20 biologics by sales only, all payers	2009-2019	12% to 20%, varies by product	$10 billion (2.4% of baseline spending)
Grabowski et al., 2007 as applied in Goodman et al., 2009 (sensitivity analysis)	Economic model	6 major categories of biologics, top 20 biologics by sales only, all payers	2009-2019	12% to 40%, varies by product	$1 billion to $44 billion (0.2% to 10.5% of baseline spending)
Ahlstrom et al., 2007 (Avalere Health)	Actuarial model	Federal payers only	2008-2017	10% to 51%, varies by product and increasing over time	$3.6 billion (0.6% of baseline spending)
Engel and Novitt, 2007	Actuarial model	Excludes Enhanced Primary Care, Medicare Part B only (office-based, physician-administered biologics)	2007-2016	Unknown	$14.4 billion
Miller and Houts, 2007 (Express Scripts)	Actuarial model	Select markets, all commercial payers	2007-2016	25%	$71 billion (baseline not reported)
Congressional Budget Office, 2008	Actuarial model	All biologics	2009-2018	20% to 40%, varies by product and increasing over time	$25 billion (baseline not reported), $7 billion of which accrues to the federal government
Shapiro et al., 2008	Actuarial model	Top 12 biologic classes	2010-2019	25% to 35%, varies by assumption	$67 billion to $108 billion

Source: Mulcahy, Predmore, and Mattke, 2014.

efficient for several reasons, reflecting gains from several sources. First, via biosimilarity, some of the redundant clinical testing and the associated expenditures are eliminated. In addition, competition necessitates more efficient production, lower costs, and savings, all of which are passed on to patients. In the small molecule arena, this has created a robust, successful US generic industry and 75 percent of all prescriptions dispensed are now generics (Lybecker, 2014; Lybecker, 2016).

It is important to note that early evidence in Europe did suggest that a rapid erosion of prices could be possible. According to a 2016 study, "Contrary to initial market expectations, Europe is seeing rapid erosion of net prices in several drug categories that are closer to what is typically seen with small molecule generics, where prices can erode by 70-80% roughly six months after loss of exclusivity. The erosion is due to a combination of factors, including increased competition and growing support of biosimilars" (Schafer, Tapella, and Kantarelis, 2016). The study cites discounts for Erythropoeitin at 81 percent in Croatia, Infliximab at 69 percent in Norway and 70 percent in Denmark, as well as the European average of 31 percent across all biosimilars (Schafer, Tapella, and Kantarelis, 2016).

The European experience is particularly important since the EU first embraced biosimilars and has approved more drugs, more quickly, than other jurisdictions. The EU's lead suggests that the European experience may foretell pricing patterns in other markets, including Canada. Table 6 below describes the biosimilars approved by Health Canada. This may be compared with those approved in the European Union, the United States, and Australia, as presented in Tables 7 to 9 in Appendix A.

As a final caveat, it is important to note that the Patented Medicines Price Review Board (PMPRB) regulates only the prices pharmaceutical companies charge wholesalers, pharmacies, or hospitals. The agency has no oversight of consumer prices (Lepage, 2015).

Market Failures in the Biopharmaceutical Industry

Knowledge-intensive industries are unique from other modern economic sectors and they face very specific challenges. Moreover, the biopharmaceutical industry is distinct from other knowledge-intensive industries in some very particular ways. Biopharmaceutical firms specialize in the manufacture of a social good characterized by high fixed costs, substantial informational and regulatory costs, and a comparatively low marginal cost of production. The production of knowledge––as embodied in biologic therapies––is characterized by the three sources of market failure identified by Arrow (1962).

First, information has one of the classic properties of public goods and the externalities inherent to them. In economic terms, once discovered, knowledge is both non-rival and non-excludable. Biopharmaceutical innovations are easily copied[9] and sold by their competitors—the knowledge is non-rival, available to all, and undiminished by use; and it is non-excludable—the innovator cannot prevent the knowledge from being used. Given the inherent challenges in delineating and enforcing property rights to new technologies, it is difficult for innovative firms to appropriate the returns accruing from their investments. This is of particular importance since the costs of research and development are primarily fixed costs and very high—borne only by the innovator—while the marginal cost of production, the only cost faced by non-innovating producers, is relatively low. Accordingly, innovative investments may not be made, and pharmaceutical R&D will be under-produced. That is, from an overall social-welfare standpoint less research and development is conducted than would be optimal because an innovative firm's R&D is likely to confer benefits on other firms, benefits for which the innovative firm will not be compensated even under a patent system. The apparatus embodied in the patent system encourages additional pharmaceutical research and development

[9] While biologics are more difficult and more expensive to replicate than traditional small molecule pharmaceuticals, the process is still far less expensive than independent development, especially when the innovators' patented knowledge and clinical trial data may be used in seeking regulatory approval.

by guaranteeing innovators a period of exclusivity during which they are able to recover their R&D investments. Intellectual property rights protection is particularly important to biopharmaceutical innovators since these measures facilitate investment in these new technologies without which the market failures would overwhelm all incentives to invest.

A second source of market failure stems from the indivisibility of new knowledge. That is, knowledge is most usually discrete rather than continuous in nature. Specifically, some knowledge (discrete) proceeds through large gains, frequently at great expense, while other knowledge (continuous) is accumulated through small increments. A consequence of the discrete nature of new knowledge is the generation of economies of scale and scope in its production. In the biopharmaceutical industry, the research and development necessary to innovate a new therapy is characterized by a large fixed cost.

Finally, the third market failure stems from the extensive risk and degree of uncertainty surrounding the production of new knowledge. Innovation frequently requires large investments of time, talent, and resources, investments that may have to be made with little or no assurance of return. Given the uncertainty that surrounds these investments and the unpredictable nature of discovery, it may be the case that too little is invested in the production of new knowledge.

These market failures reduce the likelihood that the rate of investment in the development and diffusion of such technologies will reach the socially optimal level. Accordingly, the efficient solution is to implement policies focused on providing incentives for the development and diffusion of these technologies. This is most frequently done through intellectual property rights (IPRs) protection which provides the market exclusivity that gives firms the incentive to invest in the difficult and expensive R&D necessary for biopharmaceutical advances. This incentive system is the heart of the static/dynamic trade-off that characterizes the existing patent system. In exchange for 20 years of market exclusivity—a static loss—new knowledge is forever brought into the public domain—a dynamic gain.[10]

Due to the tremendous costs of bringing a new medicine to market, the protection granted to innovators through IPRs is disproportionally important for the biopharmaceutical industry. Recent studies estimate that the preapproval cost of developing a biologic approaches $2.6 billion and that the time needed to recover the preapproval R&D costs is between 12.9 and 16.2 years (DiMasi, Grabowski, and Hanson, 2016; Grabowski,

[10] The temporary static inefficiency results from the loss of consumer welfare due to higher prices that result from market exclusivity. In contrast, the permanent dynamic gains result from the incentives patents provide to develop new products and the knowledge that is thereby provided to society.

Long, and Mortimer, 2011). Admittedly, this calculation of the preapproval cost of development is extensively criticized and is clearly highly controversial. Nevertheless, even at half the current estimate, it remains a significant investment of both time and money. Biopharmaceutical firms seeking approval by the US FDA will have considered 5,000 to 10,000 experimental compounds over a period of 10 to 15 years, and typically only one will gain approval. In addition, only three out of every ten medicines will recoup the financing required for their development, leaving those few blockbuster products to cover the expenses of numerous failures. Innovative firms are significantly disadvantaged if other firms do not have to bear the development cost and are still able to compete and sell the drugs (Lybecker, 2016).

Intellectual Property Protection and Biologics

As described earlier, biologic medicines are fundamentally different from traditional small molecule pharmaceuticals. They therefore present new challenges in designing the intellectual property architecture that will protect them. Protecting the intellectual property (IP) of biologics is complicated, difficult, and essential to the continued development of these therapies. However, this is precisely the area of medicine that will yield the largest advances and most significant return on investment. Given this, the intellectual property elements of biologic medicines include both the chemical structure of the molecule as well as the process for how to reliably, safely, and consistently manufacture the molecule at scale in living tissues (Ezell, 2012). As such, product patents alone are insufficient for protecting biologics and providing the incentives for their development. Due to the large molecule nature of biologic products, product patent protection is often narrower than that of small molecule drugs. That is, the significant molecular size of biologic products makes it easier to "invent around" an existing patent, thus narrowing the extent of coverage for the innovation. In essence, the complexity of biologic products makes it easier to design around the protected elements of the drug. Accordingly, process patents are proportionally more important. "Unlike small-molecule manufacturing, biomanufacturers get approval for both the drug and the process used to make it, and that approval can take years" (McCook, 2005: 1). Within the United States and according to FDA guidelines, "Issuance of a biologics license is a determination that the product, *the manufacturing process, and the manufacturing facilities* [emphasis added] meet applicable requirements to ensure the continued safety, purity and potency of the product" (US FDA, 2015: 1).

Patents protect traditional small molecule drugs for a 20-year term. However, because of to their complexity, size, and the large number of similar effective variants, biologic therapies are more challenging to comprehensively protect with patents (Stroud, 2013). While critical to protecting the intellectual property of biologics, neither product nor process patents are able to protect the intellectual property of the innovator

firm's safety and efficacy data, developed through proprietary preclinical and clinical trial results.[11] This information must be protected with data exclusivity provisions, protection which provides a period of time following marketing approval during which competing firms may not use the innovative firm's clinical trial data on the product's safety and efficacy, in order to obtain marketing authorization for a generic version, as in the case of traditional small molecule drugs. At the point when the compound first shows medicinal promise, the generation and collection of this data is expensive in both time and financial resources. Data exclusivity grants the innovative firm a period of protection for their investment in clinical trials and data collection, regardless of the length of time necessary to bring the drug to market.

Although complementary, data exclusivity protection and patents serve distinct purposes and give incentives for innovation in different ways. Patents protect innovations ranging from breakthrough discoveries to incremental improvements, protecting inventions that meet the standards of patentability and are determined to be novel, nonobvious, and useful. Due to the lengthy drug-development and patent-approval processes, effective patent terms rarely correspond to regulatory approval. Accordingly, innovative biologic therapies may experience patent expiry shortly after making it to market. In contrast, data exclusivity protects the tremendous resources required for clinical testing and trials, which are needed to establish a new therapy as safe and effective. Data exclusivity protection requires competing firms seeking regulatory approval of the same or a similar product to independently produce the comprehensive preclinical and clinical trial data rather than rely on or use the innovator's data. Clearly this involves a significant investment for the competing firm, an investment that may be avoided if the competing firm waits the set period of time before using the innovator's prior approval in an abbreviated regulatory approval.

Importantly, data exclusivity is not an extension of patent rights, nor does it preclude a third party from introducing a generic version of the innovator's therapy during the data exclusivity period, provided that the

[11] Both product and process patents are used to protect traditional small molecule pharmaceuticals. In addition, data exclusivity protection provides the innovator with a period of protection for clinical trial data during which generic manufacturers are unable to use this data in seeking regulatory and market approval. For small molecule drugs, data exclusivity is frequently a shorter period of time (five years in the United States, upon marketing approval) than the period being sought to protect biologics. However, in Canada, under the data protection provisions of the Food and Drug Regulations, biologic medicines are eligible for the same eight-year term of data exclusivity as regular drug molecules, with the potential for a six-month paediatric extension upon submitting eligible clinical trials.

innovator's data are not used to secure marketing approval. This complementary protection necessitates that biosimilar manufacturers independently conduct the comprehensive preclinical and clinical trials for their own products or wait out the period of data protection before requesting a regulatory shortcut to approval based on the innovator's prior approval and data. This protection both gives biopharmaceutical firms the incentive to invest in establishing the safety and efficacy of their product and prevents competitors from free-riding on these efforts, while also ensuring patient safety, especially given the sensitivity and complexity of biologic medicines (Zuhn, 2013).

In a recent analysis, Grabowski et al. (2011) examined the appropriate length of data exclusivity, using a financial model to determine how long the exclusivity period must be to provide a typical pioneer biologic a positive return on investment. An appropriate period of protection is essential if the promise of biologics is to come to fruition. Their study draws on a representative portfolio of pioneer biologics, and they find that the break-even period ranges from 13 to 16 years.

The Canadian Landscape

Health Canada regulates biosimilars as new drugs under the Food and Drugs Act and the Food and Drug Regulations. Drug manufacturers must provide information to Health Canada demonstrating that the biosimilar and the reference biologic drug are highly similar in order to obtain authorization for a biosimilar. In addition, they must show that there are no clinically meaningful differences in terms of safety and efficacy between the originator biologic and the biosimilar. Health Canada then relies upon a benefit/risk assessment after considering all of the data submitted by the manufacturer in order to determine whether they will authorize a biosimilar for sale (Health Canada, 2019a).

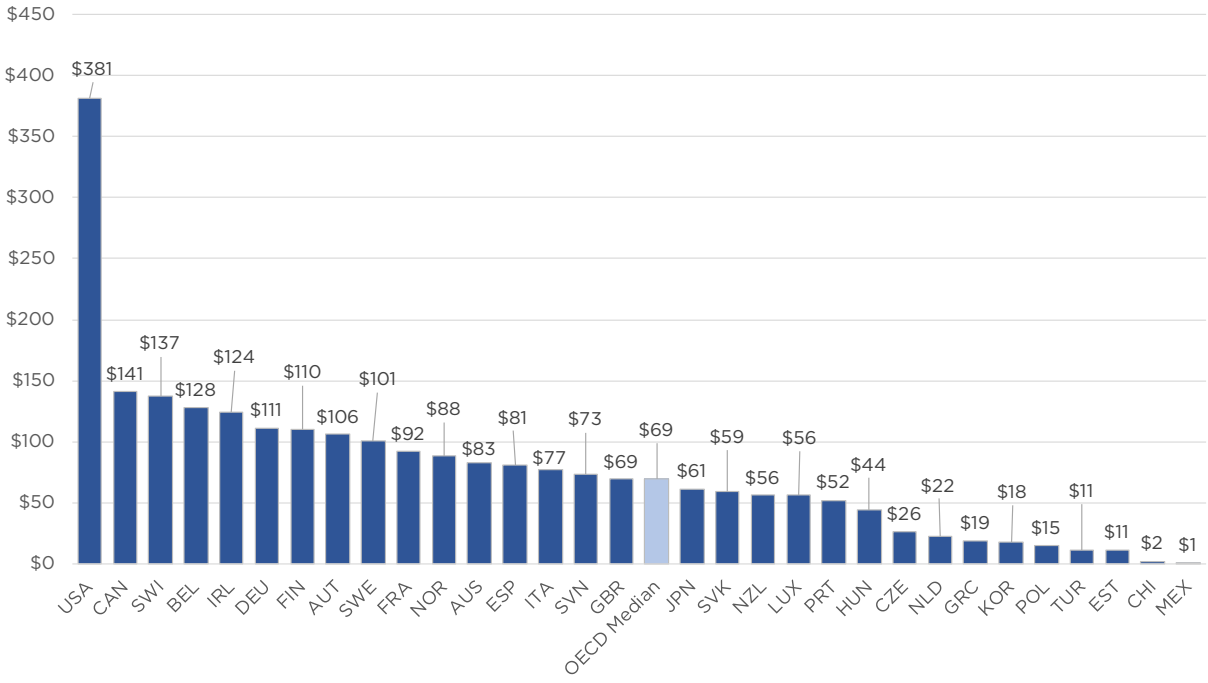
Health Canada unveiled its regulatory guidelines for the entry of biosimilars into the Canadian market in 2010, which were then revised in November 2016. In February 2018, CADTH streamlined the biosimilar review process, reducing the number of submission requirements and shortening the review period (Lungu, 2019). Notably, Health Canada harmonized its guidance for the authorization of biosimilars with the European Medicines Agency (EMA).

> "The guidance document is intended to reflect Health Canada's policy within the existing regulatory framework of its Food and Drug Regulations. As such, the guidance is an administrative instrument that provides Health Canada with flexibility in its approach to approving [biosimilars], but it does not have the force of law. When seeking marketing authorization, [a biosimilar] manufacturer is required to submit a new drug submission, which is reviewed by the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada. The manufacturer must demonstrate similarity between the [biosimilar] and its reference product such that any differences in quality attributes do not adversely impact either the safety or the efficacy of the [biosimilar]. The guidance document indicates that a combination of analytical testing, biological assays, non-clinical data, and clinical data is used in the final determination of similarity. However, the weight of the evidence should be provided by the analytical and biological characterizations of the [biosimilar]. Sponsors are referred to the product class-specific guidance documents developed by the EMA, be-

> cause the scientific principles are consistent with those of Health Canada. Health Canada plans to evaluate the implementation of its guidance document once [biosimilars] have been authorized and used in Canada for a period of time.
>
> As described by CADTH, the European Medicines Agency (EMA) Regulatory Framework, "The EMA has been the global leader in establishing the approval framework for [biosimilars]. In 2006, the EMA issued centralized, overarching guidelines outlining the quality of, non-clinical requirements for, and clinical requirements for [biosimilar] submissions to the European Union. These guidelines are supplemented by product class-specific guidance for biologics containing monoclonal antibodies, recombinant follicle-stimulating hormone, interferon beta, recombinant erythropoietin, low-molecular- weight heparins, recombinant interferon alfa, recombinant granulocyte-colony stimulating factor, somatropin, and recombinant human insulin and insulin analogues. The EMA has also issued a number of other scientific guidelines relevant to [biosimilar] evaluation including immunogenicity and comparability guidelines. The EMA evaluates every [biosimilar] application on a case-by-case basis in a tailor-made development program. The guiding principle of the regulatory framework is to establish similarity between the [biosimilar] and its reference product, ensuring that the previously proven safety and efficacy of the reference product also applies to the [biosimilar]. This is accomplished through a stepwise comparability exercise, starting with a comprehensive physiochemical and biological characterization. The extent and nature of the non-clinical and clinical studies required depend on the level and robustness of the evidence obtained in the physiochemical, biological, and non-clinical studies. The agency is currently revising its overarching guidelines for the non-clinical and clinical evaluation of [biosimilars]. Draft versions of the revised guidelines have been released for stakeholder consultation and feedback by the end of 2013." (CADTH, 2014)

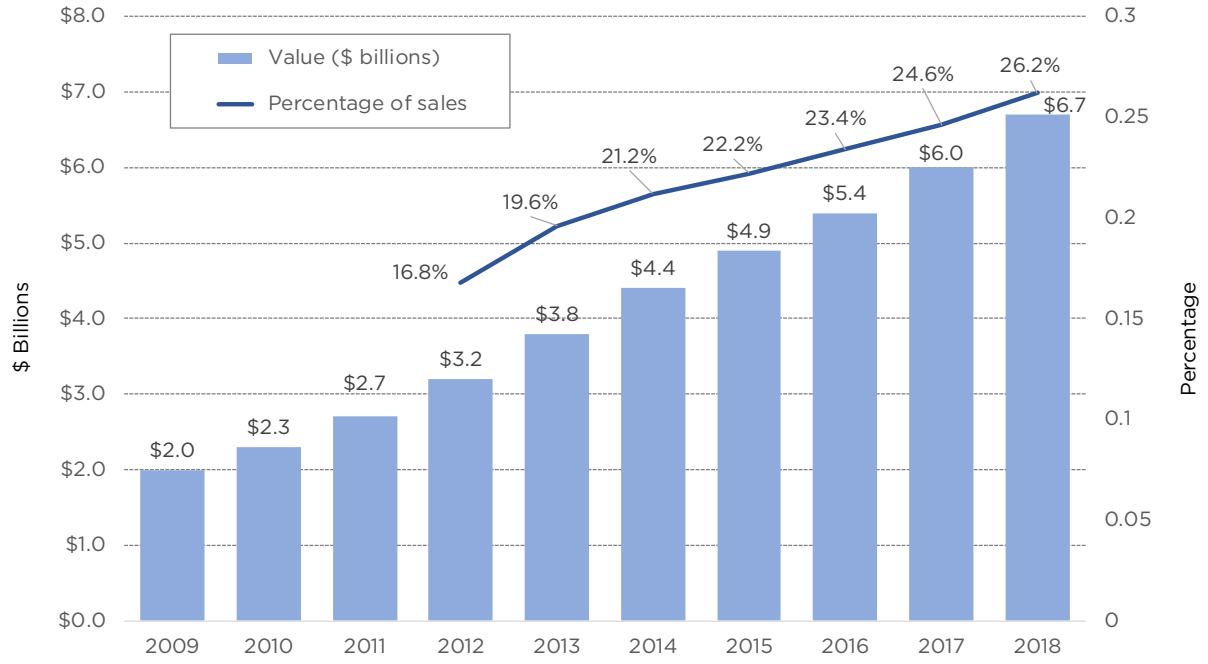
While biosimilar products first appeared in Canada in 2009 with the approval of Omnitrope (somatropin), uptake has been slow and to date Health Canada has approved fewer than a dozen biosimilars (White, Lipkus, and Maddox, 2019). Interchangeability allows one product to be substituted for another product at the time of dispensing, and these decisions are made by each province or territory according to its own regulations (CADTH, 2019). This detail is particularly relevant in the context of initiatives in BC and Alberta to expand the use of biosimilars by replacing

Figure 2: Per Capita Spending in the OECD on Patented Biologics in 2018



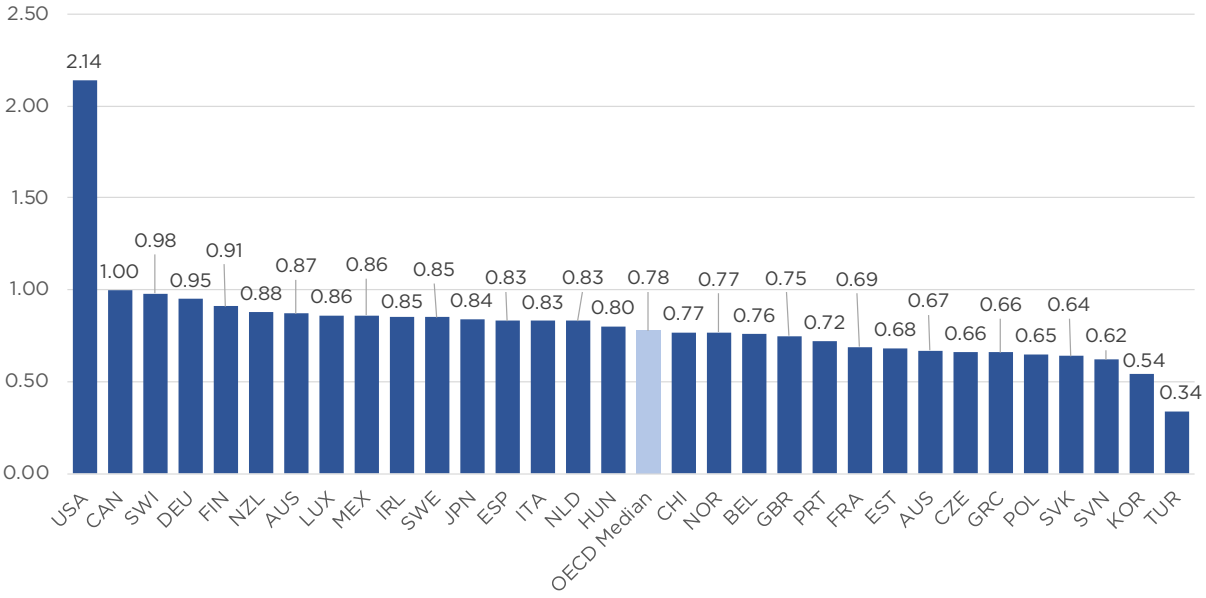
Source: Lungu, 2019.

Figure 3: Patented Biologic Sales in Canada 2009 to 2018 (in $ Billions; and as a Share of All Pharmaceutical Sales)



Source: Lungu, 2019.

Figure 4: Average 2018 Foreign-to-Canadian Price Ratios for Patented Biologics



Source: Lungu, 2019. (Note: this includes the biologics patented in Canada in 2017.)

the use of biologic drugs with their biosimilar versions whenever possible. Switching is mandatory: patients who are taking the originator biologics for the health conditions listed must switch to the biosimilar version of the drug. Of particular importance is the fact that the entity mandating the substitution also benefits financially from the switch (Alberta, 2020; British Columbia, 2020).

Canada has the second highest per-capita spending on biologics, behind the United States (Lungu, 2019), as figure 2 illustrates. Moreover, as figure 3 shows, biologic sales are increasing.

Further, Canada faces the second highest prices for biologics, behind the United States (Lungu, 2019), as is depicted in figure 4.

As noted earlier, Canada has rejected the four-letter suffixes adopted by the US Food and Drug Administration (FDA) for naming biosimilars and biologics. While identification of biosimilars and biologics is particularly important for prescribing, dispensing, and reporting adverse drug reactions, Canada will accomplish this with a unique Drug Identification Number (DIN). Within Canada, the naming convention for biologic medicines and biosimilars consists of a "unique brand name, as well as the non-proprietary (common/proper) name, without the addition of a product-specific suffix" (Health Canada, 2019b).) The World Health Organization (WHO) assigns the International Nonproprietary Name (INN)

to the active ingredient. Notably, reference biologics and biosimilars share the same non-proprietary name though they are distinguished by their unique brand names and other product-specific identifiers such as the Drug Identification Number. The unique DIN captures product information such as brand name, manufacturer name, ingredients, dosage form, strength, and route of administration (Health Canada, 2019b; Davio, 2019; Inserro, 2019).

Relative to other industrialized nations, Canada currently has one of the shortest terms of data exclusivity for pre-clinical and clinical trials. In Canada, both small molecule pharmaceuticals and biologics are given eight years of data exclusivity. This contrasts with the European Union where, similar to small molecule pharmaceuticals, biologics receive 10 years of data exclusivity, and the United States where biologics enjoy extended data protection for 12 years (Daley and Wall, 2014). While the amended United States–Mexico–Canada Agreement (USMCA or CUSMA) originally included provisions for extending the term of data protection from eight to 10 years, that obligation was removed in December 2019. Only biologic drugs whose primary patent provides less than 10 years of market exclusivity would have benefited from the change. The extension would have aligned Canadian protections with those of the European Union and would have enhanced the incentives for development of biologic medicines in Canada (Bagnoli and Bergeron, 2019).

While Canada possesses many strengths in the life science arena—world-class talent, outstanding universities, a strong health care system, and a rigorous regulatory framework—the existing gaps in the IP architecture significantly weaken its competitiveness. The Canadian interpretation of the utility standard has been particularly controversial. Canada's unique misinterpretation of the utility standard[12] resulted in the revocation of 18 patents on the basis that they were not "useful" following their approval by the Canadian health regulatory agency as safe and effective. While the drugs were in wide use by Canadian patients, the Canadian companies that sought to revoke the patents are now marketing the same medicines to patients (Loney, 2014). Beyond the interpretation of the internationally accepted utility standard, the Canadian system is characterized by onerous patentability requirements which narrow the scope of inventions, a deficient pharmaceutical-related patent enforcement and resolution mechan-

[12] Since 2005, Canadian courts have applied the "promise doctrine" such that a patented invention must actually deliver what the inventor promised (claimed or implied) it would do at the time of making the patent application, in order to satisfy the utility requirement. The promise doctrine is especially challenging for the biopharmaceutical industry since patent applications are made at an early stage, frequently before the innovator is able to accurately identify the effect of the drug.

ism under the Notice of Compliance (NOC) procedure, the lack of patent term restoration, and poor application and enforcement of civil remedies and criminal penalties (GIPC, February 2015).

As described by the Pugatch Consilium (2015), Canada's national biopharmaceutical environment has both strengths and weaknesses.[13] The key areas of strength include:

- High quality scientific and clinical research capabilities
- Regulatory standards in line with international best practices
- Quite strong quality control framework for manufacturing and distribution

Several key areas of weakness include:

- Mediocre IP environment that deviates from international norms in patenting and enforcement
- Overly restrictive and somewhat hostile P&R (pricing and reimbursement) environment
- Some delays in the regulatory system
- High costs and remaining gap between industry and research institutions impede drug discovery and development reaching full R&D potential

Current biosimilar products in Canada

Beginning in 2009, Health Canada approved numerous biosimilars for the Canadian market. Table 6 identifies the approved products across Canada, the United States, Europe, and Australia as of December 2018. Appendix A provides additional details on each of these approvals. The table starkly illustrates Canada's small number of approvals; the number in the United States is also lower than in Europe.

[13] Canada's low score in effective intellectual property protection results from several factors. First, "Canada continues to have the shortest data exclusivity term, potentially allowing biosimilars to enter the Canadian market before the US and EU markets" (Daley and Wall, 2014: 1). In addition, the Canadian government should grant innovative pharmaceutical companies an effective right to appeal an adverse court decision on a patent challenge. At this time, in the case of a patent challenge, generic manufactures have the right to appeal an adverse court ruling, while innovative companies do not. Providing innovative companies an effective right of appeal would restore fairness and balance and put Canada within the mainstream of international intellectual property law.

Table 6: Approved Products Across Canada, the United States, Europe, and Australia, as of December 2018

Nation	Product name	Active substance	Authorization date	Withdrawn	Canada (10)	US (15)	EU (62)	Australia (20)
USA	Amjevita (adalimumab-atto)	adalimumab	2016-09-23			X		
EU	Solymbic	adalimumab	2017-03-22				X	
EU	Imraldi	adalimumab	2017-08-24				X	
USA	Cyltezo (adalimumab-adbm)	adalimumab	2017-08-25			X		
Australia	Amgevita	adalimumab	2017-11-09					X
Australia	Hadlima	adalimumab	2018-01-24					X
Canada	Hadlima	adalimumab	2018-05-08		X			
EU	Halimatoz	adalimumab	2018-07-26				X	
EU	Kromeya	adalimumab	2019-04-02				X	
EU	Idacio	adalimumab	2019-04-03				X	
EU	Cyltezo	adalimumab	10 Nov 2017	X			X	
EU	Hulio	adalimumab	17 Sep 2018				X	
EU	Amgevita	adalimumab	22 Mar 2017				X	
EU	Hefiya	adalimumab	26 Jul 2018				X	
EU	Hyrimoz	adalimumab	26 Jul 2018				X	
USA	Mvasi (bevacizumab-awwb)	bevacizumab	2017-09-14			X		
EU	Mvasi	bevacizumab	2018-01-15				X	
Canada	Mvasi	bevacizumab	2018-10-17		X			
EU	Zirabev	bevacizumab	2019-02-14				X	
EU	Inhixa	enoxaparin sodium	2016-09-15				X	
EU	Thorinane	enoxaparin sodium	2016-09-15				X	
EU	Abseamed	epoetin alfa	2007-08-28				X	
EU	Binocrit	epoetin alfa	2007-08-28				X	
EU	Epoetin alfa Hexal	epoetin alfa	2007-08-28				X	
USA	Retacrit (epoetin alfa-epbx)	epoetin alfa	2018-05-15			X		
Australia	Aczicrit	epoetin lambda	2010-01-27					X
Australia	Grandicrit	epoetin lambda	2010-01-27					X
Australia	Novicrit	epoetin lambda	2010-01-27					X
EU	Retacrit	epoetin zeta	2007-12-18				X	
EU	Silapo	epoetin zeta	2007-12-18				X	
EU	Benepali	etanercept	2016-01-14				X	
Australia	Brenzys	etanercept	2016-07-22					X
USA	Erelzi (etanercept-szzs)	etanercept	2016-08-30			X		
Canada	Brenzys	etanercept	2016-08-31		X			

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Table 6: Approved Products Across Canada, the United States, Europe, and Australia, as of December 2018

Nation	Product name	Active substance	Authorization date	Withdrawn	Canada (10)	US (15)	EU (62)	Australia (20)
EU	Erelzi	etanercept	2017-06-27				X	
Canada	Erelzi	etanercept	2017-08-03		X			
Australia	Erelzi	etanercept	2017-11-30					X
EU	Filgrastim ratiopharm	filgrastim	2008-09-15	X			X	
EU	Ratiograstim	filgrastim	2008-09-15				X	
EU	Tevagrastim	filgrastim	2008-09-15				X	
EU	Filgrastim Hexal	filgrastim	2009-02-06				X	
EU	Zarzio	filgrastim	2009-02-06				X	
EU	Nivestim	filgrastim	2010-06-08				X	
Australia	Nivestim#	filgrastim	2010-09-16					X
Australia	Tevagrastim#	filgrastim	2011-08-29					X
Australia	Zarzio#	filgrastim	2013-05-07					X
EU	Grastofil	filgrastim	2013-10-18				X	
EU	Accofil	filgrastim	2014-09-18				X	
USA	Zarxio(filgrastim-sndz)	filgrastim	2015-03-06			X		
Canada	Grastofil	filgrastim	2015-12-07		X			
USA	Nivestym (filgrastim-aafi)	filgrastim	2018-07-20			X		
EU	Biograstim	filgrastim	15 Sep 2008	X			X	
EU	Ovaleap	follitropin alfa	2013-09-27				X	
EU	Bemfola	follitropin alfa	2014-03-24				X	
Australia	Bemfola	follitropin alfa	2015-11-27					X
EU	Inflectra	infliximab	2013-09-10				X	
EU	Remsima	infliximab	2013-09-10				X	
Canada	Inflectra	infliximab	2014-01-15		X			
Canada	Remsima	infliximab	2014-01-15		X			
Australia	Inflectra#	infliximab	2015-08-19					X
EU	Flixabi	infliximab	2016-05-26				X	
Australia	Renflexis	infliximab	2016-11-28					X
USA	Renflexis (infliximab-abda)	infliximab	2017-04-21			X		
USA	Ixifi (infliximab-qbtx)	infliximab	2017-12-13			X		
Canada	Renflexis	infliximab	2018-03-22		X			
EU	Zessly	infliximab	2018-05-24				X	
USA	Inflectra (infliximab- dyyb)	infliximab	5 Apr 2016			X		
Australia	Basaglar	insulin glargine	2014-11-21					X
USA	Basaglar#	insulin glargine	2015-12-16			X		

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Table 6: Approved Products Across Canada, the United States, Europe, and Australia, as of December 2018

Nation	Product name	Active substance	Authorization date	Withdrawn	Canada (10)	US (15)	EU (62)	Australia (20)
EU	Lusduna	insulin glargine	2017-01-04				X	
USA	Lusduna# (tentative approval)	insulin glargine	2017-07-20			X		
EU	Semglee	insulin glargine	2018-03-28				X	
Australia	Semglee	insulin glargine	2018-03-28					X
EU	Abasaglar (previously Abasria)	insulin glargine)	2014-09-09				X	
USA	Admelog#	insulin lispro	2017-12-11			X		
EU	Insulin lispro Sanofi	Insulin lispro	19 Jul 2017				X	
Canada	Lapelga	pegfilgrastim	2018-04-05		X			
USA	Fulphila (pegfilgrastim-jmdb)	pegfilgrastim	2018-06-04			X		
EU	Pelgraz	pegfilgrastim	2018-09-20				X	
EU	Fulphila	pegfilgrastim	2018-11-20				X	
EU	Pelmeg	pegfilgrastim	2018-11-23				X	
EU	Ziextenzo	pegfilgrastim	2018-11-27				X	
EU	Udenyca	pegfilgrastim	20 Sep 2018				X	
EU	Pegfilgrastim Mundipharma	pegfilgrastim	CHMP positive opinion 17 October 2019				X	
EU	Truxima	rituximab	2017-02-17				X	
EU	Rixathon	rituximab	2017-06-19				X	
EU	Blitzima	rituximab	2017-07-13				X	
EU	Ritemvia	rituximab	2017-07-13				X	
EU	Rituzena (previously Tuxella)	rituximab	2017-07-13				X	
Australia	Riximyo	rituximab	2017-11-30					X
Australia	Truxima	rituximab	2018-04-16					X
EU	Riximyo	rituximab	15 Jun 2017				X	
EU	Omnitrope	somatropin	2006-04-12				X	
EU	Valtropin	somatropin	2006-04-24	X			X	
Canada	Omnitrope	somatropin	2009-04-20		X			
Australia	Omnitrope	somatropin	2010-09-29					X
Australia	SciTropin A	somatropin	2010-09-29					X
EU	Somatropin Biopartners	somatropin	2013-09-09	X			X	
EU	Terrosa	teriparatide	2017-01-04				X	
EU	Movymia	teriparatide	2017-01-11				X	

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Table 6: Approved Products Across Canada, the United States, Europe, and Australia, as of December 2018

Nation	Product name	Active substance	Authorization date	Withdrawn	Canada (10)	US (15)	EU (62)	Australia (20)
EU	Ontruzant	trastuzumab	2017-11-15				X	
USA	Ogivri (trastuzumab-dkst)	trastuzumab	2017-12-01			X		
EU	Herzuma	trastuzumab	2018-02-09				X	
Australia	Herzuma	trastuzumab	2018-07-17					X
EU	Trazimera	trastuzumab	2018-07-26				X	
EU	Ogivri	trastuzumab	2018-12-12				X	
EU	Kanjinti	trastuzumab	2018-05-16				X	

Listed in the Australian Pharmaceutical Benefits Scheme (PBS).

Source: GaBi, August 2018 and December 2018(a, b, c).

Conclusions

According to Walsh (2018), accounting for withdrawals, the number of individual biopharmaceutical products with current active licenses is 316, and those 316 are essentially revolutionizing the pharmaceutical industry. Biologic medicines are transforming the lives of patients across the globe, and they are poised to become ever more important in the years to come. Current growth trends promise increasing value in the future and a shift by the biopharmaceutical industry toward devoting a growing proportion of their research and development pipelines to biologics. This shift also brings great hope for patients since biologics have greater on-target efficiency and lower risk of off-target toxicity relative to traditional small molecule pharmaceuticals (Meininger, 2014).

Both the creation and regulation of biologic medicines differ in important ways from traditional so-called "small molecule" drugs. Biologics are highly sensitive to their manufacturing and handling conditions, as well as their physical environment. As such, biologics are more difficult to chemically characterize and to manufacture than small molecule drugs, such that even minor differences in production processes or cell lines can generate variations in the resulting protein. Consequently, quality control is even more critical and production complications are potentially more catastrophic than in the production of traditional small molecule drugs. The differences and how they are addressed are critically important in determining the future of health care and the treatment patients will receive for decades to come.

History teaches that technology evolves faster than the legal architecture that surrounds it. The continued development of biologic medicines hinges on global intellectual property protection. Patent protection and data exclusivity protections are both essential for efficiently ensuring that companies have the incentives to develop biologics.

Biopharmaceutical firms specialize in the manufacture of a social good characterized by high fixed costs, substantial informational and regulatory costs, and a comparatively low marginal cost of production. Biopharmaceutical innovations are easily copied and sold by their competitors—the knowledge is non-rival, available to all and undiminished by use, and non-excludable (the innovator cannot prevent the knowledge

from being used). Given the inherent challenges in delineating and enforcing property rights to new technologies, it is difficult for innovative firms to appropriate the returns accruing from their investments.-

Due to the tremendous costs of bringing a new medicine to market, the protection granted to innovators through intellectual property rights is disproportionally important for the biopharmaceutical industry. Moreover, the intellectual property elements of biologic medicines include both the chemical structure of the molecule and the process for reliably, safely, and consistently manufacturing the molecule at scale in living tissues. While critical to protecting the intellectual property of biologics, neither product nor process patents are able to protect the intellectual property of the innovator firm's safety and efficacy data, developed through proprietary preclinical and clinical trial results. This information must be protected with data exclusivity provisions. As technology changes to enable the development of new biologic vaccines and therapies, intellectual property protection must also evolve to ensure sufficient protection for these products.

As the market for biologic medicines has matured, biosimilars have entered the market. The creation of biosimilars is considerably different from the creation of generic versions of traditional small molecule drugs. Unlike generic small molecule drugs, biosimilars are not identical to the reference biologic. As such, questions arise surrounding interchangeability, a standard that differs across countries and regions. In Canada, interchangeability is a provincial decision. It is critical to be very cautious with automatic substitution and conservative in the extrapolation of indications, since great uncertainty surrounds how the process of substituting a biosimilar for its pioneer reference product can affect patients' immune systems.

Canada's protection of intellectual property in the life sciences significantly lags behind that provided by many other industrialized nations, including the United States, the EU, and Japan. Canada currently has one of the shortest terms of data exclusivity for pre-clinical and clinical trials. Canada's unique misinterpretation of the utility standard is also a significant barrier to biopharmaceutical innovation.

This study introduces biologic medicines and biosimilars. It explores some of the challenges and controversies that uniquely characterize their production, regulation, and marketing. The primer presents an overview of the basics of biologics and biosimilars, and discusses how biologics differ from traditional small molecule pharmaceuticals. The primer also explores the differences between biosimilars and traditional generic drugs. It emphasizes the importance of precision in biologic development and manufacture, and considers salient features of production and mar-

ket characteristics. In addition, the study focuses on the market failures present in the biopharmaceutical industry and the role of intellectual property rights in ensuring that the promise of biologic medicine is realized. Finally, the paper presents a description of the Canadian specifics for the biopharmaceutical industry. Understanding both the promise and the challenges of biologic medicines is valuable for patients and policymakers alike. If we are to realize the benefits of these therapeutic advances, we must ensure that there are sufficient incentives for companies to develop them, and that they are precisely developed, responsibly manufactured, and effectively brought to those who need them.

Appendix A: Supplementary Tables

The following four tables identify the biosimilars approved for the US, EU and Australian markets. Table 7 depicts US FDA approved biosimilars (as of August 2018), table 8 depicts those approved by the European Medicines Agency (as of December 2018), table 9 depicts those approved by Australia's Therapeutic Goods Administration (as of December 2018), and table 10 depicts those approved by Health Canada (as of August 2018).

Table 7: US FDA-Approved Biosimilars and Follow-On Biologicals*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Admelog#	insulin lispro	Diabetes	11-Dec-17	Sanofi
Amjevita (adalimumab-atto)	adalimumab	Ankylosing spondylitis Crohn's disease Juvenile arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	23-Sep-16	Amgen
Basaglar#	insulin glargine	Diabetes	16-Dec-15	Eli Lilly/ Boehringer Ingelheim
Cyltezo (adalimumab-adbm)	adalimumab	Ankylosing spondylitis Crohn's disease Juvenile arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	25-Aug-17	Boehringer Ingelheim
Erelzi (etanercept-szzs)	etanercept	Axial spondyloarthritis Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis	30-Aug-16	Sandoz
Fulphila (pegfil-grastim-jmdb)	pegfilgrastim	Febrile neutropenia	4-Jun-18	Biocon/Mylan
Inflectra (infliximab- dyyb)	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	5 Apr 2016	Pfizer (Hospira)
Ixifi (infliximab-qbtx)	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	13-Dec-17	Pfizer

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Table 7: US FDA-Approved Biosimilars and Follow-On Biologicals*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Lusduna# (tentative approval)	insulin glargine	Diabetes	20-Jul-17	Merck
Mvasi (bevacizumab-awwb)	bevacizumab	NSCLC Colorectal neoplasms Renal cell carcinoma Ovarian neoplasms Breast neoplasms	14-Sep-17	Amgen/Allergan
Nivestym (filgrastim-aafi)	filgrastim	Autologous peripheral blood progenitor cell collection and therapy	20-Jul-18	Pfizer (Hospira)
Ogivri (trastuzumab-dkst)	trastuzumab	HER2 breast cancer HER2 metastatic gastric or gastroesophageal junction adenocarcinoma	1-Dec-17	Biocon/Mylan
Retacrit (epoetin alfa-epbx)	epoetin alfa	Anaemia (chronic kidney disease, Zidovudine, chemotherapy) Reduction of allogeneic red blood cell transfusions	15-May-18	Pfizer (Hospira)
Renflexis (infliximab-abda)	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	21-Apr-17	Samsung Bioepis
Zarxio (filgrastim-sndz)	filgrastim	Autologous peripheral blood progenitor cell collection and therapy Bone marrow transplantation Cancer Myeloid leukaemia Neutropenia	6-Mar-15	Sandoz

*Data updated August 31, 2018.

#Admelog, Basaglar and Lusduna were approved via the FDA's abbreviated 505(b)(2) pathway as follow-on products, not as biosimilars. No insulin lispro or glargine products were licensed under the Public Health Service Act at the time of filing, so there was no "reference product" for a proposed biosimilar product.

NSCLC: Non-Small-Cell Lung Carcinoma.

Source: GaBi, August 2018.

Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Abasaglar (previously Abasria)	insulin glargine	Diabetes	9-Sep-14	Eli Lilly/Boehringer Ingelheim
Abseamed	epoetin alfa	Anaemia Cancer Chronic kidney failure	28-Aug-07	Medice Arzneimittel Pütter
Accofil	filgrastim	Neutropenia	18-Sep-14	Accord Healthcare
Amgevita	adalimumab	Ankylosing spondylitis Crohn's disease Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	22 Mar 2017	Amgen
Benepali	etanercept	Axial spondyloarthritis Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis	14-Jan-16	Samsung Bioepis
Bemfola	follitropin alfa	Anovulation (IVF)	24-Mar-14	Finox Biotech
Binocrit	epoetin alfa	Anaemia Chronic kidney failure	28-Aug-07	Sandoz
Biograstim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008 Withdrawn on Dec 22, 2016	CT Arzneimittel
Blitzima	rituximab	Non-Hodgkin lymphoma Chronic B-cell lymphocytic leukaemia	13-Jul-17	Celltrion
Cyltezo	adalimumab	Crohn's disease Hidradenitis suppurativa Juvenile idiopathic arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Uveitis	10 Nov 2017 Withdrawn on January 15, 2019	Boehringer Ingelheim
Epoetin alfa Hexal	epoetin alfa	Anaemia Cancer Chronic kidney failure	28-Aug-07	Hexal

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Erelzi	etanercept	Ankylosing spondylitis Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis	27-Jun-17	Sandoz
Filgrastim Hexal	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	6-Feb-09	Hexal
Filgrastim ratiopharm	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15-Sep-08 Withdrawn on 20 Apr 2011	Ratiopharm
Flixabi	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	26-May-16	Samsung Bioepis
Fulphila	pegfilgrastim	Neutropenia	20-Nov-18	Mylan
Grastofil	filgrastim	Neutropenia	18-Oct-13	Apotex
Halimatoz	adalimumab	Ankylosing spondylitis Hidradenitis suppurativa Juvenile rheumatoid arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Uveitis	26-Jul-18	Sandoz
Hefiya	adalimumab	Ankylosing spondylitis Hidradenitis suppurativa Juvenile rheumatoid arthritis Psoriasis Uveitis	26 Jul 2018	Sandoz
Herzuma	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	9-Feb-18	Celltrion Healthcare

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Hulio	adalimumab	Ankylosing spondylitis Crohn's Disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative Colitis Uveitis	17 Sep 2018	Mylan/Fujifilm Kyowa Kirin Biologics
Hyrimoz	adalimumab	Ankylosing spondylitis Crohn's Disease Hidradenitis suppurativa Juvenile rheumatoid arthritis Papulosquamous skin disease Psoriatic arthritis Rheumatoid arthritis Ulcerative Colitis Uveitis	26 Jul 2018	Sandoz
Idacio	adalimumab	Ankylosing spondylitis Arthritis Crohn's Disease Hidradenitis suppurativa Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	3-Apr-19	Fresenius Kabi
Imraldi	adalimumab	Ankylosing spondylitis Arthritis Crohn's Disease Hidradenitis suppurativa Psoriatic arthritis, Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	24-Aug-17	Samsung Bioepis

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Inflectra	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10-Sep-13	Hospira
Inhixa	enoxaparin sodium	Venous thromboembolism	15-Sep-16	Techdow Europe
Insulin lispro Sanofi	Insulin lispro	Diabetes mellitus	19 Jul 2017	Sanofi-Aventis
Kanjinti	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	16 May 2018	Amgen/Allergan
Kromeya	adalimumab	Ankylosing spondylitis Arthritis Crohn's Disease Hidradenitis suppurativa Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	2-Apr-19	Fresenius Kabi
Lusduna	insulin glargine	Diabetes	4-Jan-17	Merck (MSD)
Movymia	teriparatide	Osteoporosis	11-Jan-17	Stada Arzneimittel
Mvasi	bevacizumab	Breast neoplasms Fallopian tube neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Peritoneal neoplasms Renal cell carcinoma	15-Jan-18	Amgen
Nivestim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	8-Jun-10	Hospira (Pfizer)
Ogivri	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	12-Dec-18	Biocon/Mylan

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Omnitrope	somatropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome	12-Apr-06	Sandoz
Ontruzant	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	15-Nov-17	Samsung Bioepis
Ovaleap	follitropin alfa	Anovulation (IVF)	27-Sep-13	Teva Pharma
Pegfilgrastim Mundipharma	pegfilgrastim	Neutropenia	CHMP positive opinion Oct. 17, 2019	Mundipharma Biologics
Pelgraz	pegfilgrastim	Neutropenia	20-Sep-18	Accord Healthcare
Pelmeg	pegfilgrastim	Neutropenia	23-Nov-18	Cinfa Biotech/ Mundipharma
Ratiograstim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15-Sep-08	Ratiopharm
Remsima	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10-Sep-13	Celltrion
Retacrit	epoetin zeta	Anaemia Autologous blood transfusion Cancer Chronic kidney failure	18-Dec-07	Hospira
Ritemvia	rituximab	Wegener granulomatosis Microscopic polyangiitis Non-Hodgkin Lymphoma	13-Jul-17	Celltrion
Rituzena (previously Tuxella)	rituximab	Wegener granulomatosis Microscopic polyangiitis Non-Hodgkin Lymphoma Chronic B-cell lymphocytic leukaemia	13-Jul-17	Celltrion

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Rixathon	rituximab	Chronic B-cell lymphocytic leukaemia Microscopic polyangiitis Non-Hodgkin Lymphoma Rheumatoid arthritis Wegener granulomatosis	19-Jun-17	Sandoz
Riximyo	rituximab	Chronic B-cell lymphocytic leukaemia Microscopic polyangiitis Non-Hodgkin Lymphoma Rheumatoid arthritis Wegener granulomatosis	15 Jun 2017	Sandoz
Semglee	insulin glargine	Diabetes	28-Mar-18	Mylan
Silapo	epoetin zeta	Anaemia Autologous blood transfusion Cancer Chronic kidney failure	18-Dec-07	Stada Arzneimittel
Solymbic	adalimumab	Ankylosing spondylitis Crohn's disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	22-Mar-17	Amgen
Somatropin Biopartners	somatropin	Pituitary dwarfism Turner syndrome	9-Sep-13 Withdrawn on Dec. 1, 2017	BioPartners
Terrosa	teriparatide	Osteoporosis	4-Jan-17	Gedeon Richter
Tevagrastim	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15-Sep-08	Teva Generics
Thorinane	enoxaparin sodium	Venous thromboembolism	15-Sep-16	Pharmathen
Trazimera	trastuzumab	Stomach Neoplasms Breast Neoplasms	26-Jul-18	Pfizer

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Table 8: European Medicines Agency Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Truxima	rituximab	Chronic lymphocytic leukaemia Granulomatosis with polyangiitis Microscopic polyangiitis Non-Hodgkin's lymphoma Rheumatoid arthritis	17-Feb-17	Celltrion
Udenyca	pegfilgrastim	Neutropenia	20 Sep 2018	ERA Consulting (Coherus Biosciences)
Valtropin	somatropin	Pituitary dwarfism Turner syndrome	24-Apr-06 Withdrawn on May 10, 2012	BioPartners
Zarzio	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	6-Feb-09	Sandoz
Zessly	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis psoriasis Rheumatoid arthritis Ulcerative colitis	24-May-18	Sandoz
Ziextenzo	pegfilgrastim	Neutropenia	27-Nov-18	Sandoz
Zirabev	bevacizumab	Breast neoplasms Fallopian tube neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Peritoneal neoplasms Renal cell carcinoma	14-Feb-19	Pfizer

*Data collected on 12 May 2011, updated on 25 October 2019

CHMP: Committee for Medicinal Products for Human Use; VF: in vitro fertilization.

Sources: EMA; GaBi, December 2018a.

Table 9: Australia's Therapeutic Goods Administration Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date**	Manufacturer/ Company name
Aczicrit	epoetin lambda	Anaemia Cancer Chronic kidney failure	27-Jan-10	Sandoz
Amgevita	adalimumab	Ankylosing spondylitis Crohn's Disease Enthesitis-related arthritis Hidradenitis suppurativa Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	9-Nov-17	Amgen
Basaglar	insulin glargine	Diabetes	21-Nov-14	Eli Lilly Australia
Bemfola	follitropin alfa	Infertility treatment	27-Nov-15	Finox Biotech
Brenzys	etanercept	Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis	22-Jul-16	Samsung Bioepis
Erelzi	etanercept	Ankylosing spondylitis Juvenile idiopathic arthritis Paediatric psoriasis Psoriatic arthritis Psoriasis Rheumatoid arthritis	30-Nov-17	Novartis
Grandicrit	epoetin lambda	Anaemia Cancer Chronic kidney failure	27-Jan-10	Sandoz
Hadlima	adalimumab	Rheumatoid arthritis	24-Jan-18	Samsung Bioepis
Herzuma	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	17-Jul-18	Celltrion Healthcare
Inflectra#	infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	19-Aug-15	Hospira (Pharmbio)

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Table 9: Australia's Therapeutic Goods Administration Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date**	Manufacturer/ Company name
Nivestim#	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	16-Sep-10	Hospira
Novicrit#	epoetin lambda	Anaemia Cancer Chronic kidney failure	27-Jan-10	Novartis Pharmaceuticals Australia
Omnitrope#	somatropin	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	29-Sep-10	Sandoz
Renflexis	infliximab	Ankylosing spondylitis Crohn's disease Rheumatoid arthritis Psoriasis Psoriatic arthritis Ulcerative colitis	28-Nov-16	Samsung Bioepis
Riximyo	rituximab	B-cell NHL Chronic lymphocytic leukaemia Microscopic polyangiitis Rheumatoid arthritis Wegener's granulomatosis	30-Nov-17	Sandoz Australia
SciTropin A	somatropin	Growth disturbance due to chronic renal insufficiency Pituitary dwarfism Turner syndrome	29-Sep-10	SciGen Australia
Semglee	insulin glargine	Diabetes	28-Mar-18	Biocon
Tevagrastim#	filgrastim	Cancer Haematopoietic stem cell trans-plantation Neutropenia	29-Aug-11	Aspen Pharmacare Australia
Truxima	rituximab	B-cell NHL Chronic lymphocytic leukaemia Microscopic polyangiitis Rheumatoid arthritis Wegener's granulomatosis	16-Apr-18	Celltrion

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Table 9: Australia's Therapeutic Goods Administration Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date**	Manufacturer/ Company name
Zarzio#	filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	7-May-13	Sandoz

*Data updated 31 August 2018

**Date listed on Australian Register of Therapeutic Goods (ARTG); #Listed in the Australian Pharmaceutical Benefits Scheme (PBS)

NHL: non-Hodgkin's lymphoma.

Source: GaBi, December 2018(c).

Table 10: Health Canada Approved Biosimilars*

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer/ Company name
Brenzys	etanercept	Ankylosing spondylitis Rheumatoid arthritis	31-Aug-16	Merck Canada
Erelzi	etanercept	Ankylosing spondylitis Juvenile idiopathic arthritis Rheumatoid arthritis	3-Aug-17	Sandoz
Grastofil	filgrastim	Neutropenia	7-Dec-15	Apotex
Hadlima	adalimumab	Rheumatoid arthritis	8-May-18	Samsung Bioepis
Inflectra	infliximab	Ankylosing spondylitis Crohn's disease# Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis#	15-Jan-14	Hospira
Lapelga	pegfilgrastim	Neutropenia	5-Apr-18	Apotex
Mvasi	bevacizumab	Colorectal cancer NSCLC	17-Oct-18	Amgen
Omnitrope	somatropin	Growth hormone deficiency in adults and children	20-Apr-09	Sandoz
Remsima	infliximab	Crohn's disease# Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis#	15-Jan-14	Celltrion
Renflexis	infliximab	Crohn's disease Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	22-Mar-18	Samsung Bioepis

*Data collected on 23 January 2014, updated on 14 December 2018

#Added to approved indications on 14 June 2016

NSCLC: Non-small cell lung cancer.

Sources: Health Canada; GaBi, December 2018b.

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