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The Biologics Revolution in the Production of Drugs

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Executive summary

To date, almost 200 biologic medicines have been brought to market. It is projected that by 2017, biologics could comprise seven of the top ten global pharmaceuticals and account for up to 30 percent of pharmaceuticals under development. This study is an introduction to biologic medicines and to some of the issues and controversies that are unique to their production, regulation, and marketing.

Biologics are defined as “a large molecule typically derived from living cells and used in the treatment, diagnosis, or prevention of disease. Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies, and fusion proteins.” Specifically, most biologic medicines are developed using recombinant DNA (rDNA) technology. They are produced by genetically engineering living cells to create the required proteins rather than through traditional chemical synthesis.

Biologics are highly sensitive to the conditions in which they are manufactured and handled, 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.

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 (that is, 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 (IP) rights is disproportionately important for the biopharmaceutical indus-

try. 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 the market for biologic medicines matures, generic versions—properly known in Canada as subsequent entry biologics or SEBs—will enter the market. The creation of subsequent entry biologics is considerably different from the creation of generic versions of traditional small molecule drugs. Unlike generic small molecule drugs, subsequent entry biologics are not identical to the pioneer 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 there is great uncertainty about how the process of substituting a subsequent entry biologic 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 what is known as the utility standard is also a significant barrier to biopharmaceutical innovation. Through the promise doctrine, Canada is the only developed country in the world with a patent utility standard that is inconsistent with both NAFTA and TRIPS. The promise doctrine causes significant uncertainty for innovators because it requires the innovator both "soundly predict" how the invention will be used and also provide sufficient information in the patent application to establish that the invention will successfully fulfill its promise. Increased levels of IP protection are needed in order to provide the incentives for investment in new breakthrough therapies and cures.

Several issues remain for future research. These include determining the most effect means of protecting the intellectual property embodied in biologics, establishing the best mechanism for how biologics and subsequent entry biologics should be named, estimating the cost savings that will result from the use of SEBs, and developing a safe and effective policy on the interchangeability and substitutability of subsequent entry biologics with their pioneer reference products.

Introduction

The pharmaceutical industry has been revolutionized by the development of biologic medicines. Biologics (large molecule drugs usually derived from living cells) 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.¹ 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.

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 benefiting 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 Convention on Biological Diversity of 1992. Under Article 16 of the convention, biotechnology is defined as “any

¹ Biopharmaceuticals are currently produced using one of two technology platforms and the active chemical substances 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 by 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).

technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use” (United Nations, 1992).

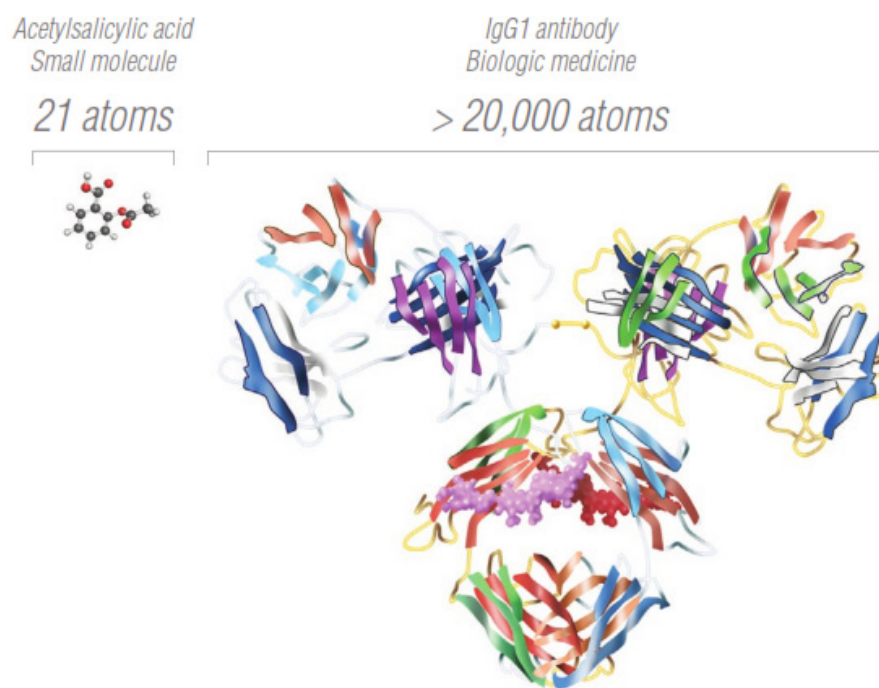
This paper is intended as an introduction to biologic medicines and to some of the issues and controversies that are unique to their production, regulation, and marketing. The study begins with an overview of the basics, a discussion of how biologics differ from traditional small molecule pharmaceuticals, and an answer to the question, “What are biologics?” This is followed by a discussion of the precision required in the development and manufacture of biologics and an explanation of why exactness is so important in this industry. Next, the paper describes the market failures that characterize innovative industries in general and biologics in particular. This directly segues into a discussion of the importance of intellectual property rights protection in the biopharmaceutical industry. The paper then presents a comparison of the markets for small molecule generic drugs and non-innovator biologics. Then it describes the Canadian environment surrounding the biopharmaceutical industry. Finally, the paper concludes and outlines a number of the issues that remain for future research.

Biologic Medicines: The Basics

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.

Biologic medicines represent one of the most promising frontiers in medicine. But with the promise of great progress comes the significant challenges of developing and manufacturing these medicines. Biologics are defined as “a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease. Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies, and fusion proteins” (Amgen, 2012: 5). Specifically, most biologic medicines are developed using recombinant DNA (rDNA) technology. They are produced by genetically engineering living cells to create the required proteins rather than using traditional chemical synthesis. They are created by adapting or exploiting the processes found inside living organisms, and manufactured inside animal cells or micro-organisms such as bacteria or yeast (*The Economist*, 2015). The result is that biologics are considerably larger than small molecule drugs, often 200 to 1000 times their size. Moreover, biologics are significantly more complex structurally. This translates into medicines that are much more sensitive than small molecule drugs to even minute changes in the manufacturing process, which can alter their nature and therapeutic functions. Figure 1, below, contrasts the complexity and structure of a conventional small molecule drug, with a biologic.

Figure 1: Comparison of Small Molecule Pharmaceuticals and Biologics



Source: Amgen, 2014. Image used with permission of Amgen Inc.

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).

In order to fully understand the distinction between small molecule pharmaceuticals and biologics, it is critical to establish why and in what ways biologics differ. The first important difference between small molecule medicines and biologics is based in their chemical structures. The chemical structures of traditional small molecule pharmaceuticals are commonly well defined. Accordingly, laboratory analysis is generally able to precisely determine the complete composition of the drug, so replica-

Table 1: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Pharmaceuticals	Biologics
Method of Synthesis	Chemical synthesis	Genetically engineering living organisms or cells
Molecular Size	Small	Large
Structure	Usually fully known	Complex, Frequently partially unknown
Susceptibility to Contamination during Manufacturing	Low	High
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)
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 (ie., Absorption, Distribution, Metabolism, and Excretion)		
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*	Frequently Linear	Usually Non-linear
Half-life	Short(er)	Long
Safety	Toxicity (variable mechanisms)	Exaggerated pharmacology**

Source: Klein & Wang, 2013; Lybecker, 2014.

* PK = pharmacokinetics, the branch of pharmacology devoted to the absorption, distribution, metabolism, and elimination of pharmacological substances in the body. “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 doses” (Birkett, 1994: 36).

** 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).

tion (generic production) is quite straightforward. In contrast, biologic medicines are very difficult and sometimes impossible to characterize scientifically due to the complexity of their chemical structure. Perhaps surprisingly, a number of the components of a finished biologic may be unknown (BIO, 2010a). For obvious reasons this significantly complicates the production of generic versions of biologics.² Accordingly, the FDA has struggled to establish “interchangeability” for complex proteins.³

The distinctions between small molecule pharmaceuticals and biologics go far beyond their relative sizes and structural complexity. Table 1 describes a number of dimensions along which the two differ, as well as what these specific differences are.

As described above, due to their structural complexity, the difficulty of chemical replication, and the precision required in the manufacturing process, biologic medicines are distinct from small molecule pharmaceuticals in important ways. While biologics promise a new frontier in medicine, a number of challenging issues surround their production and marketing, as well as the protection of their intellectual property rights. The following section addresses some of the challenges in developing and manufacturing biologics.

² While generic versions of small molecule drugs may be produced to exactly replicate the chemical structure of the innovator drug, this is impossible for biologic medicines. Non-innovator versions of biologics are not chemically equivalent to the originator drug. For this reason, subsequent versions of a drug produced by firms other than the innovator are known as biosimilars, follow-on biologics (FOBs), or subsequent entry biologics (SEBs). They are molecules that are similar, but not identical, to the pioneer biologic. A more substantial discussion of the differences between generic small molecule drugs and subsequent entry biologics is provided in the later section “Small molecule generics and subsequent entry biologics.”

³ Interchangeable biologic products are highly similar to an already-approved biological product (the biological reference product), and are expected to produce the same clinical result as the biological reference product in any given patient.

The Precise Development and Manufacture of Biologics

As described above, biologics are highly sensitive to their manufacturing and handling conditions, as well as their physical environment. As Amgen describes it:

The genetic code of a chosen protein, such as human insulin or an immune system antibody, is identified and replicated by combining different segments of DNA to build a functional DNA sequence. The DNA sequence is introduced into the host cell of a living organism, such as bacteria, yeast or mammal cells, altering the cell's genetic makeup and coding it to produce the chosen protein. Genetically modified cell lines are carefully selected and cultured in large bioreactors before the biologic medicine is extracted through complex and lengthy purification processes. (Amgen, 2014)

Each of the thousands of steps in the process described above is intricate, highly delicate, and requires precise technique. 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 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 (Greenmeier, 2008). Importantly, immunogenicity problems may result

from even minute changes made by the pioneering company under strictly controlled conditions. Consider the case of EPREX 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, 2010b).

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 increasing

value and prevalence of biologics in the pipeline of the biopharmaceutical industry.

Good manufacturing processes and quality control issues are critical for all medicines, and even more so for biologics. Accordingly, the growing share of imported medicines and off-shore 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 (Canada, 2015) 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, recent safety lapses are tremendously worrisome: Health Canada recently 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.

The Value of Biologics

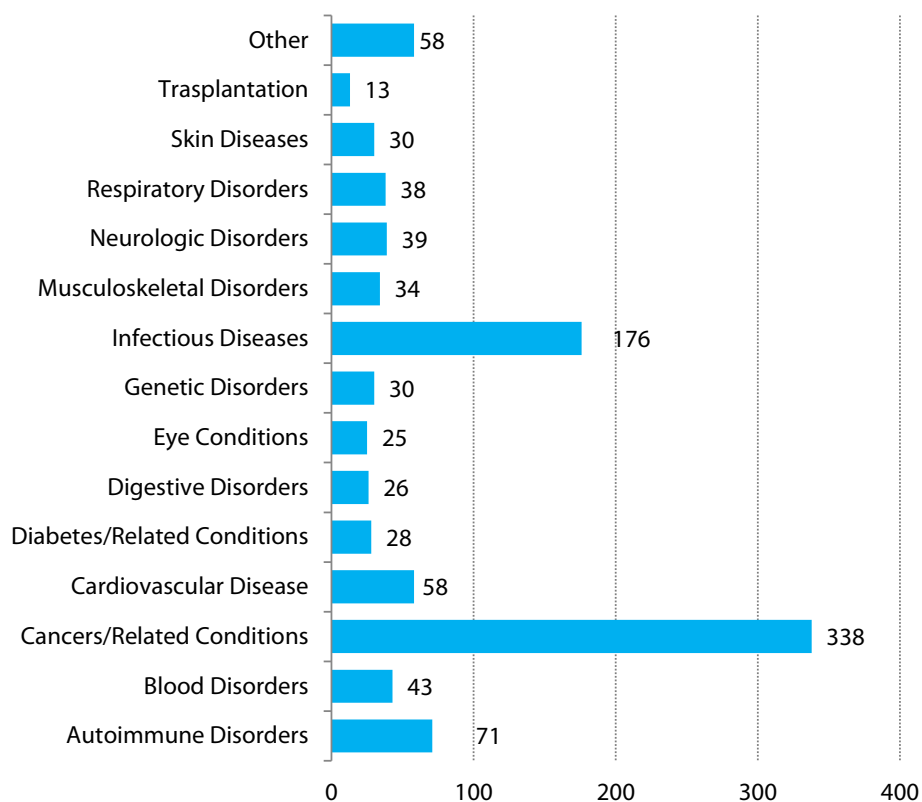
To date, more than 250 biologic therapies and vaccines have transformed the lives of hundreds of millions of patients (BIO, 2015). In the United States, more than 900 biologics are currently in development for more than 100 diseases (*The Economist*, 2015). Figure 2 describes these efforts by therapeutic category. Of these projects in development, 70 percent of drugs across the pipeline are potential first-in-class medicines (PhRMA, 2013a).⁴

Not surprisingly, analysts believe that by 2017 biologic medicines will comprise seven of the top ten global pharmaceuticals and that 30 percent of the pharmaceutical industry pipeline will be biologics (Sandoz, n.d.). It is important to note that the effective patent lives of these medicines differ due to the amount of time needed to bring them to market. When clinical trials can be completed more quickly, more of the drug's patent term remains, providing a longer effective patent life once the drug is brought to market.

These medicines are developed with an understanding of the mechanisms of diseases, such that the biologics can target and modify the underlying causes. This may allow the treatment to 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*, 2015).

Current estimates suggest that biologics provided close to 22 percent of the sales of large pharmaceutical firms in 2013, and expectations are that this will rise to 32 percent by 2023 (*The Economist*, 2015). Moreover, in 2011, global spending on biologic medicines increased 7 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. Biologic sales

⁴ A first-in-class drug program is technologically new, one that is on the cutting edge of science. It is a project that is unprecedented scientifically with the goal of generating the first type of drug of its kind (LaMattina, 2013).

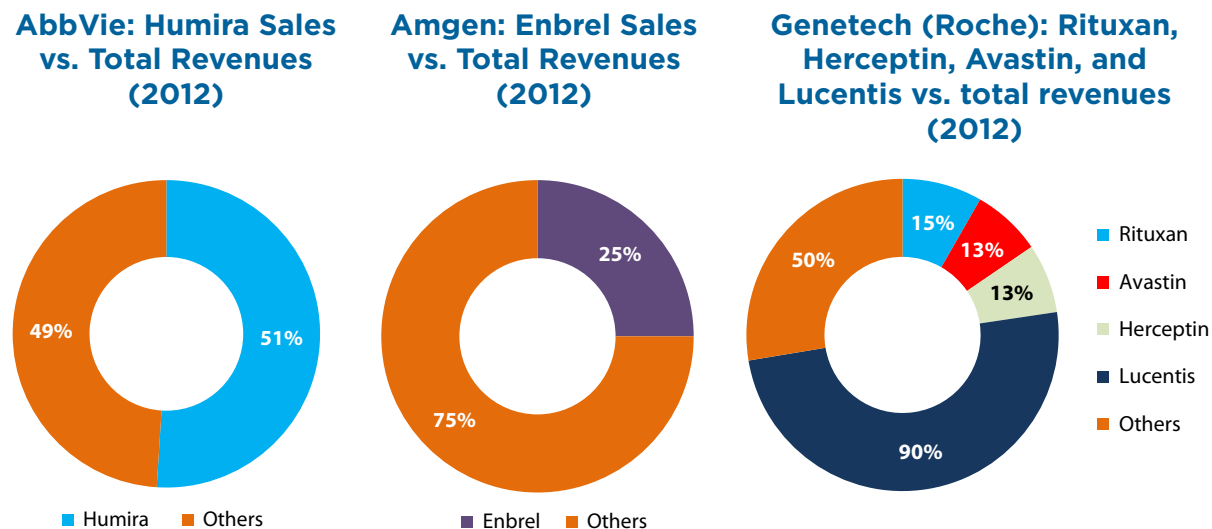
Figure 2: Biologic Medicines in Development in 2013

Source: PhRMA, 2013a.

Note: Some medicines are being explored in more than one therapeutic category.

are dominated by the United States, with a market share of 43 percent, followed by the European Union, at 21 percent, and Japan, at 9 percent (White, 2014). Within the United States, spending on specialty drugs increased four-fold from 2006 to 2014, and it is estimated that by 2018 these specialty drugs will account for 1 percent of all US prescriptions, but fully 50 percent of all prescription costs (Express Scripts, 2014). Currently, biologics cost an average of 22 times that of non-biologic drugs. The costs of these drugs continues to generate significant controversy in the US where the pricing of Sovaldi, used in the treatment of Hepatitis C, has drawn considerable criticism from health advocates, payers, and politicians. To that point, while biologics currently account for less than one percent of all US prescriptions, they comprise 28 percent of prescription drug expenditures (Sarpatwari, Avorn, and Kesselheim, 2015).

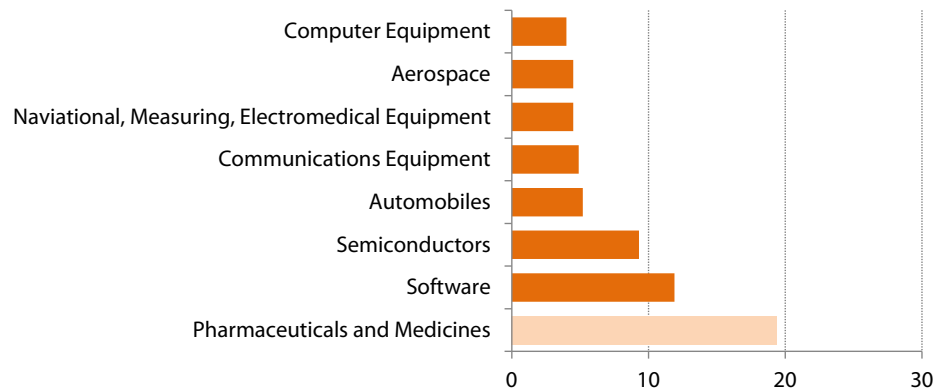
As biologics grow in market share importance, their sales are an increasingly important source of revenues for biopharmaceutical firms.

Figure 3: The Importance of Biologics

Source: White, 2014.

Figure 3 depicts the share revenues generated by biologics for three industry leaders, AbbVie, Amgen, and Genentech, in 2012.

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 US sales totaling \$60 billion will lose patent protection in the US market (Silverman, 2015). Beyond patent expiry, these revenues are also threatened by increasing scrutiny from government health agencies and other payers. As reported by *The Economist* (2015), the governments of Italy and France have taken note that Avastin, a biologic developed for cancer, also treats macular degeneration. Moreover, 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*, 2015). A similar situation exists in Canada, where the prevalence of off-label use is estimated at 11 percent; and of the off-label prescriptions, 79 percent lacked strong scientific evidence (Egual, 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

Figure 4: Share of Total U.S. Business R&D by Sector, 2008

Source: PhRMA, 2013a.

“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 it may pose to patients (Rawson, 2015). This seems to indicate that cost-containment is more important in Canada’s public drug plans than incentivizing innovation or patient health.

Beyond the value of biologics to public health and longevity, innovation is crucial to trade and economic prosperity. Figure 4 demonstrates that the biopharmaceutical sector is the single largest funder of business research and development (R&D) in the United States, representing nearly 20 percent of all domestic R&D.⁵ Moreover, each direct biopharmaceutical job supports five additional jobs in other sectors, such that the 650,000 US biopharmaceutical jobs support a total of four million US jobs (PhRMA, 2013a). As evidence of the importance of the innovation-intensive sectors to the US economy, in 2011 IP-intensive industries exported more than \$1 trillion in goods and services, which accounts for approximately 74 percent of total 2011 US exports (Pham, 2012). The biopharmaceutical industry in the United States is the fourth-largest US exporter among IP-intensive industries, with exports valued at \$49.4 billion in 2010 (Economics and Statistics Administration and the United States Patent and Trademark Office, 2012).

⁵ This includes producers of both biologics and small molecules.

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 copied⁶ and sold by their competitors—the knowledge is non-rival (i.e., available to all and undiminished by use), and non-excludable (i.e., the innovator cannot prevent the knowledge from being used). Given the inherent challenges to new technologies in delineating and enforcing property rights, 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 and very high—and are borne only by the innovator—while the marginal cost of production, the only cost faced by non-innovating producers, is relatively low. Because of this, 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

⁶ 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 innovator's patented knowledge and clinical trial data may be used in seeking regulatory approval.

embodied in the patent system encourages additional pharmaceutical research and development 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, new 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, these economies of scale stem from the large fixed cost necessary to fund the research and development necessary to innovate a new therapy.

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. This is particularly the case in the biopharmaceutical industry.

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 the protection of intellectual property rights (IPRs), which provides the market exclusivity that gives firms the incentives 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.⁷

Due to the tremendous costs of bringing a new medicine to market, the protection granted to innovators through IPRs is disproportionately

⁷ 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.

Figure 5: Trends in Clinical Trial Protocol Complexity

	2000-2003	2008-2011	Percentage Change
Total Procedures per Trial Protocol (median) (e.g., bloodwork, routine exams, x-rays, etc.)	105.9	166.6	57%
Total Investigative Site Work Burden (median units)	28.9	47.5	64%
Total Eligibility Criteria	31	46	58%
Clinical Trial Treatment Period (median days)	140	175	25%
Number of Case Report Form Pages per Protocol (median)	55	171	227%

Source: PhRMA, 2013a.

Note: The complexity of the clinical trials results from a variety of factors including a shift in focus from acute to chronic illness, the collection of increasingly intricate data elements, closer attention to each element of trial design, and concern about potential requests from regulatory agencies (Getz, Campo, and Kaitin, 2011).

important for the biopharmaceutical industry. Recent studies estimate that the preapproval cost of developing a biologic approaches \$1.2 billion and that the time needed to recover the preapproval R&D costs is between 12.9 and 16.2 years (DiMasi and Grabowski, 2007; Grabowski, Long and Mortimer, 2011). Admittedly, this calculation of the preapproval cost of development is extensively criticized and is clearly a highly controversial figure. Nevertheless, even at half the current estimate, it remains a significant investment of both time and money. The complexity of clinical trials and the approval process have both increased considerably, as figure 5 shows. The approval process shaves vital years off the effective patent life of these medicines. Biopharmaceutical firms seeking US Food and Drug Administration (FDA) approval 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 3 out of every 10 medicines will recoup the financing required for their development, leaving those few blockbuster products to cover the expenses of numerous failures. All the while, the uniqueness of the innovation is threatened by the fact that it is very easy to copy. Innovative firms are at a significant disadvantage if other firms do not have to bear the development cost and are still able to compete and sell the drugs.

Intellectual Property Protection and Biologics

As described above, 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 and difficult, yet essential to the continued development of these therapies. Given this, 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 (Ezell, 2012). As such, product patents alone are insufficient for protecting biologics and providing incentives for their development. Due to the large molecule nature of biologic products, product patent protection is often narrower than that for 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.⁸ 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* meet applicable requirements to ensure the continued safety, purity and potency of the product” [emphasis added] (US FDA, 2015).

Patents protect traditional small molecule drugs for a 20-year term. However, biologic therapies are more challenging to comprehensively protect with patents due to their complexity, size, and the large number of similar effective variants (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

⁸ Inventing around amounts to designing an alternative to a patented invention without infringing the patent’s claims.

trial results.⁹ This information must be protected with data exclusivity provisions, protection that 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 provide 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 innovator's data is not used to secure marketing approval. This comple-

⁹ 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 time (5 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.

mentary protection necessitates that subsequent entry biologic (SEB) 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 an incentive to biopharmaceutical firms 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 (Bioeconomy, 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.

Small Molecule Generics and Subsequent Entry Biologics

As the market for biologic medicines matures, generic versions—properly known in Canada as subsequent entry biologics or SEBs—will enter the market. The creation of subsequent entry biologics is considerably different from the creation of generic versions of traditional small molecule drugs. Similarly, the regulation of subsequent entry biologics must recognize the difficulties, technicalities, and science involved.

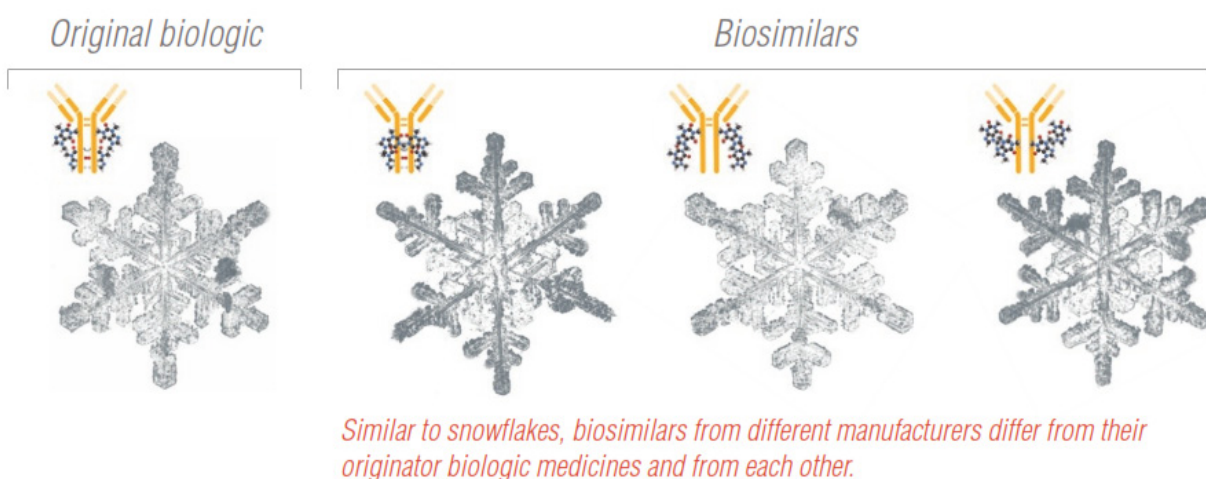
Biologics and subsequent entry biologics are not identical

In contrast to traditional small molecule pharmaceuticals, the manufacture of biological products is a vastly more difficult and complex process. Moreover, the outcome of the production process is highly contingent on precise replication—use of the same steps, equipment, and manufacturing variables are critical. As noted above, even minor differences in the final protein structure can result in a product that behaves differently than the original. “Living cells may chemically modify the proteins they make by adding complex sugars and other compounds at certain positions. The exact conditions under which cells are grown can alter the pattern of these modifications, and thus the molecule’s structure and behavior. The result is a drug so complex that it is difficult—if not impossible—to fully characterize” (Ledford, 2015). Figure 6 illustrates the differences between pioneer products and subsequent entry biologics.

In contrast to small molecule pharmaceuticals, in biologics the production process is critical to the end product. Table 2 describes many of the dimensions along which small molecule generics and subsequent entry biologics differ.

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

Figure 6: Illustrating the Differences between Original Biologics and Biosimilars



Source: Amgen, 2014. Image used with permission of Amgen Inc.

can then yield a product that diverges from its predecessor” (Sarpawari, 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 relative to 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).

Substitution and interchangeability

As described above, unlike generic small molecule drugs, subsequent entry biologics are not identical to the pioneer biologic. “An SEB sponsor can demonstrate similarity based on a combination of analytical testing, biological assays, and non-clinical and clinical data, but the weight of the evidence should be provided by analytical and biological characterization” (Daley and Wall, 2014: 1). As such, questions arise surrounding interchangeability, a standard that differs across countries and regions. “Unlike generic drugs, not all biosimilars will be deemed ‘interchangeable’ with their originator counterparts (at least initially), and nearly all biosimilars

Table 2: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Generics	Subsequent Entry Biologics
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
Comparative Clinical Trial	Not required	At least one
Indication Extrapolation	Automatic	Case by case
Regulation	Must be identical to reference product Abbreviated approval process in most countries, available for all drugs “Substitutability” status granted	Must be highly similar to reference product Abbreviated approval pathways vary depending on the drug “Comparability” status Approval pathways vary by country, still under development*
Marketing	No/Limited detailing to physicians Key role of wholesalers and payers Market substitution in pharmacies Significant price discounts	Required detailing to specialty physicians Pharmacists may not substitute Limited price discounts, price sensitivity is product specific
Interchangeability	Yes	Generally no Fifteen nations have prohibited automatic substitution Interchangeability remains a provincial decision in Canada

Source: Klein & Wang, 2013; Lybecker, 2014; First Word, 2013.

* 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, 2013, Gabl, 2014).

will require at least one head-to-head clinical trial to confirm similarity with the originator biologic as the basis for approval” (Mulcahy, Predmore, and Mattke, 2014: 2).

In the European Union, interchangeability and substitution decisions are made at the national level and 15 nations prohibit automatic substitution.¹⁰ In the United States, while the US FDA may designate a drug as interchangeable with its reference biologic, it is the individual states that determine pharmacy practice and substitution laws.¹¹ In the United States, the lack of clarity surrounding the regulations for the approval of biosimilars has slowed the development of a market for them (*The Economist*, 2015). In contrast, Health Canada does not determine interchangeability for either generic small molecule drugs or for subsequent entry biologics. In Canada, interchangeability is a provincial decision (Klein and Wang, 2013). In Canada, SEBs cannot be used as reference products for new SEBs. It is critical to be very cautious with automatic substitution and conservative in the extrapolation of indications.¹² This holds true even when a subsequent entry biologic is approved for each of the same indications as a brand-name originator, especially if clinical testing has not been carried out for each indication (GaBI, April 2015). To date, great uncertainty surrounds how the process of substituting a subsequent entry biologic for its pioneer reference product can affect patients’ immune systems. In the European Union and Canada, subsequent entry biologics are primarily approved as “stand-alone” therapies, and these nations oppose the automatic substitution of a prescribed biologic with an SEB (Dolinar, 2012).¹³ In

¹⁰ “Interchangeability refers to achievement of the same clinical result in any given patient in terms of quality, safety and efficacy when a biosimilar is switched or substituted with its respective innovator biological product, when compared to the use of the reference product alone. In principle, once the biosimilar product gains ‘interchangeable’ status, it can be automatically substituted for the prescribed biological product by the pharmacist without the consent of the prescribing physician” (Thimmaraju, Rakshambikai, Farista, and Juluru, 2015: 1).

¹¹ “A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. An interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product” (US FDA, 2016).

¹² Treatment of a particular condition, disease, or symptom.

¹³ In Canada, interchangeability is a provincial decision. Accordingly, Health Canada does not make the decision, neither for generics nor for SEBs. In a 2010 letter to

particular, the European Medicines Agency has noted that prior exposure to similar or related proteins may lead to a “pre-sensitization and cause an immune response” (Dolinar, 2012: 11). In the United States, the Center for Drug Evaluation and Research warns that the process of repeated switches has a significant potential to affect safety and effectiveness (Dolinar, 2012). As yet no non-innovator biologic has been approved as interchangeable with its pioneer reference product.

In the United States, the FDA’s Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product identifies four levels of similarity: highly similar with fingerprint-like similarity, highly similar, similar, and not similar. Importantly, even “highly similar with fingerprint-like similarity” is not the same as “identical” (Gaffney, 2014). Garde (2014) defines the four categories as follows:

- » Highly similar with fingerprint-like similarity, in which a submission is deemed nearly identical to its reference product “based on integrated, multi-parameter approaches,” according to the FDA. Such drugs would need only “targeted and selective” further study to demonstrate their biosimilarity.
- » Highly similar, which also meets the statutory standard for similarity but falls short of the above-mentioned gold standard.
- » Similar, a label that applies to drugs whose analyses were inconclusive, demanding further data or studies to figure out whether changes in manufacturing or formulation might help demonstrate similarity.
- » Not similar, the draft’s most self-explanatory tier, applies to products that don’t measure up to their references.

While the issue remains undecided, many experts believe that SEBs should not be considered pharmaceutically or therapeutically equivalent to innovator biologic products and mandatory substitution to SEBs should not be recommended. This issue is particularly important for individual Canadian provinces. Canada’s federal government does not have the jurisdiction to regulate the interchangeability of subsequent entry biologics.

provincial/territorial drug plan directors concerning its guidance on the market authorization of subsequent entry biologics, Health Canada stated: “Specialized clinical studies can be used to support therapeutic interchangeability, however, these studies are not usually done and their relevance may not be long-lasting. Over time, as sponsors of the SEB and the reference biologic drug make their own independent manufacturing changes, differences could be introduced that affect the drug products. For this reason, Health Canada does not support automatic substitution of a SEB for its reference biologic drug and recommends that physicians make only well-informed decisions regarding therapeutic interchange” (Health Canada, 2010: 2).

As such, the provinces will individually determine whether an SEB may be substituted for the innovator product, as well as whether preferential reimbursement policies will apply. This is worrisome for a number of reasons. Of particular concern is the capacity of smaller provinces that may lack expertise in biologics to make decisions regarding interchangeability. Without experts to assist in this process, the potential exists for bureaucrats to intervene, which risks substitutability mandates based on cost rather than science.

Cost of production and pricing

The differences in the production of small molecule pharmaceuticals and biologic medicines also generate very different economic outcomes for generic drug and for SEBs. In the case of small molecules, the development of a successful generic industry generated competition through which prices dropped dramatically. Much of the debate surrounding protection for biologics and competition from subsequent entry biologics centers on the mistaken belief that prices would similarly drop with the development of SEB competition. However, it is unlikely that the cost savings achieved with generic production and competition among small molecule drugs will be available with subsequent entry biologics. For conventional small molecule drugs, over the requisite three to five years in which a generic is developed, the cost to do so is approximately \$1 to \$5 million, but it results in a lower-cost alternative for patients.¹⁴ In contrast, the majority of shortcuts available to generic small molecule manufacturers will not be available to SEB producers. Industry experts anticipate subsequent entry biologic firms will have to invest in clinical trials as well as manufacturing and post-approval safety monitoring programs similar to those of the innovative biologic company. Given this, subsequent entry biologics will likely require 8 to 10 years to develop, at a cost of \$75 to \$250 million (Amgen, 2014; Kambhammettu, 2008).

Numerous studies have shown that the introduction of generic versions of small molecule pharmaceuticals can reduce prices by 90 percent relative to the branded version, which has saved US consumers alone more than \$1.5 trillion over the past decade. In contrast, the cost savings from non-innovator versions of biologic medicines are inherently

¹⁴ While innovator firms bear the full cost of pharmaceutical research and development, including the development costs of all of the molecules that fail, generic producers must only reverse engineer the innovative drug and establish its bioequivalence for approval. This translates into significantly lower development costs for generic producers (Lybecker, 2014).

Table 3: Select US 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.

limited due to the complexity of their production. This complexity both increases the costs for competitor firms and also reduces the number of potential market entrants. Table 3 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 in 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%” (Sarpawari, 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 this savings will be and how easily and quickly it 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*, 2015), while Express Scripts calculates a potential \$250 billion saving in the next decade (Express Scripts, 2014).¹⁵ Moreover, these findings are arguably economically efficient for several reasons, reflecting gains from several sources. First, through the bioequivalence provision, 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).

¹⁵ 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.

Canadian Specifics

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. A 2011 Canadian Chamber of Commerce study found that Canada provides less robust IP protections for the pharmaceutical sector than the 31 peer countries used for comparison (CIPC, 2011). This translates into direct consequences for pharmaceutical investment in Canada. Increased levels of IP protection provide incentives for investment in new breakthrough therapies and cures. In contrast to recent changes that have weakened IP protections in Canada, consider the 1987¹⁶ and 1992¹⁷ changes to Canada's Patent Act that strengthened

¹⁶ As described by the Parliament of Canada, the 1987 changes consisted of the following: "Bill C-22, which amended the Patent Act, made significant changes to the compulsory licensing system for patented medicines. The amendments guaranteed patent owners a period of protection from compulsory licences. A brand-name drug manufacturer receiving an NOC for a drug after 27 June 1986 was guaranteed 10 years of protection against compulsory licences to import and seven years' protection against compulsory licences to manufacture. Patented medicines for which NOCs had been issued on or before 27 June 1986, and for which generic drug producers had obtained either an NOC or a compulsory licence to import, but not both, were entitled to seven years' protection against compulsory licences to import. Similarly, medicines for which an NOC had been issued on or before 27 June 1986, but for which neither a compulsory licence nor a generic NOC had been issued, had eight years of protection against compulsory licences to import. Additional protection was granted to drugs invented and developed in Canada; compulsory licences to import were not available, but compulsory licences to manufacture could be issued if, within the seven years after the NOC for the drug had been issued, the inventor failed to make the drug in Canada for the purpose of completely or substantially supplying the Canadian market. Bill C-22 also changed the general patent law to provide that the term of a patent would be 20 years from the date on which a patent application was filed, rather than 17 years from the date the patent was issued. This change became effective in 1989" (Douglas and Jutras, 2008: 2-3).

¹⁷ Again, as described by the Parliament of Canada, the 1992 changes consisted of the following: "The federal government endorsed the Dunkel text. The text of the North American Free Trade Agreement (NAFTA) was finalized, with Chapter 17 largely based on, and in many instances identical to, the provisions of the then draft TRIPS

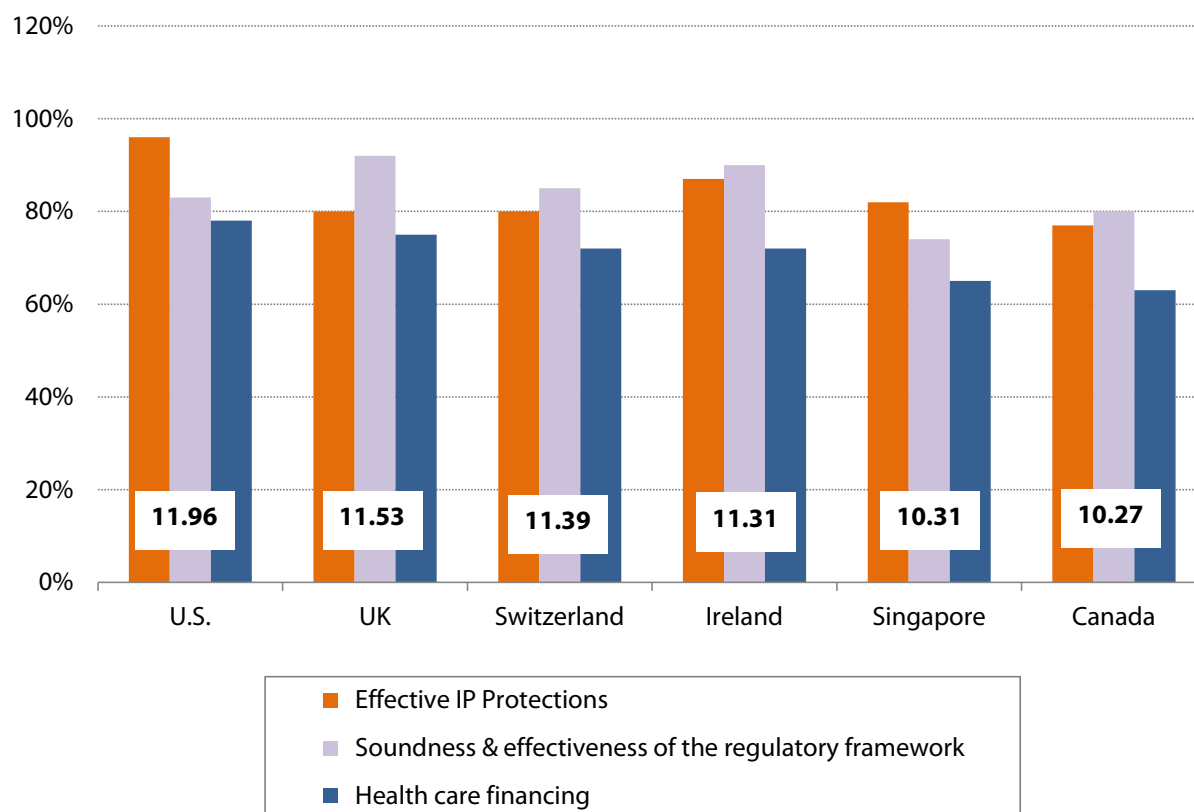
IP protection in the life sciences. The result was a 1,500 percent increase in investment in pharmaceutical research and development between 1998 and 2002 (Grootendorst and Di Matteo, 2007). Given the potential for a rigorous IP environment, Canada's existing level of intellectual property protection in the life sciences is strikingly disappointing.

Canada currently has one of the shortest terms of data exclusivity for pre-clinical and clinical trials, relative to other industrialized nations. In Canada, both small molecule pharmaceuticals, as well as 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). Canada differs from other high-income economies along other important industry dimensions as well. Figure 7 compares biopharmaceutical market access across high-income economies in the context of effective intellectual property protection, regulatory frameworks, and health care financing.

Figure 8 provides more specifics on the Canadian market, considering seven factors of critical importance to the biopharmaceutical industry. Figure 9 presents additional details on each of the areas examined in Figure 8. Canada ranks between 3rd and 7th across each of these measures.

Agreement. Article 31 of the TRIPS Agreement was reproduced almost identically in Article 1709(10) of NAFTA. The federal government moved to further modify the Patent Act and to implement the TRIPS and NAFTA provisions on intellectual property by introducing Bill C-91, the Patent Act Amendment Act, 1992, in the House of Commons. The bill eliminated compulsory licences for pharmaceutical products though compulsory licences in existence before 20 December 1991 continued in effect, subject to the seven and ten-year limitations established in Bill C-22. Compulsory licences granted after 20 December 1991 but before the day the Act came into force were terminated when the Act became effective. Bill C-91 also created two exceptions to an action for patent infringement (the rule that anyone who, without the consent of the patent owner, makes, uses or sells a product where a patent is in force is liable for patent infringement). Both exceptions permit persons to use a patented product for certain purposes before the patent expires. The first exception, known as the "early working" exception, allows a person to use a patented invention while the relevant patents are in force only for obtaining regulatory approval to sell an equivalent product after the patents have expired (section 55.2(1)). Under this provision, a generic drug manufacturer could develop a generic version of a medicine and take whatever steps were necessary to meet the regulatory requirements pertaining to its sale before the expiry of the relevant patents. The second exception ("stockpiling" exception) allows a person to use a patented invention for a period of time before the patent expires in order to manufacture and store a product intended for sale after the expiry of the patent (section 55.2(2)). Bill C-91 also provided for product patents for pharmaceutical inventions. Prior to the bill such inventions were only patentable as process patents (or so-called 'product-by-process patents') (Douglas and Jutras, 2008: 3-4).

Figure 7: Comparison of Biopharmaceutical Market Access across High-Income Economies

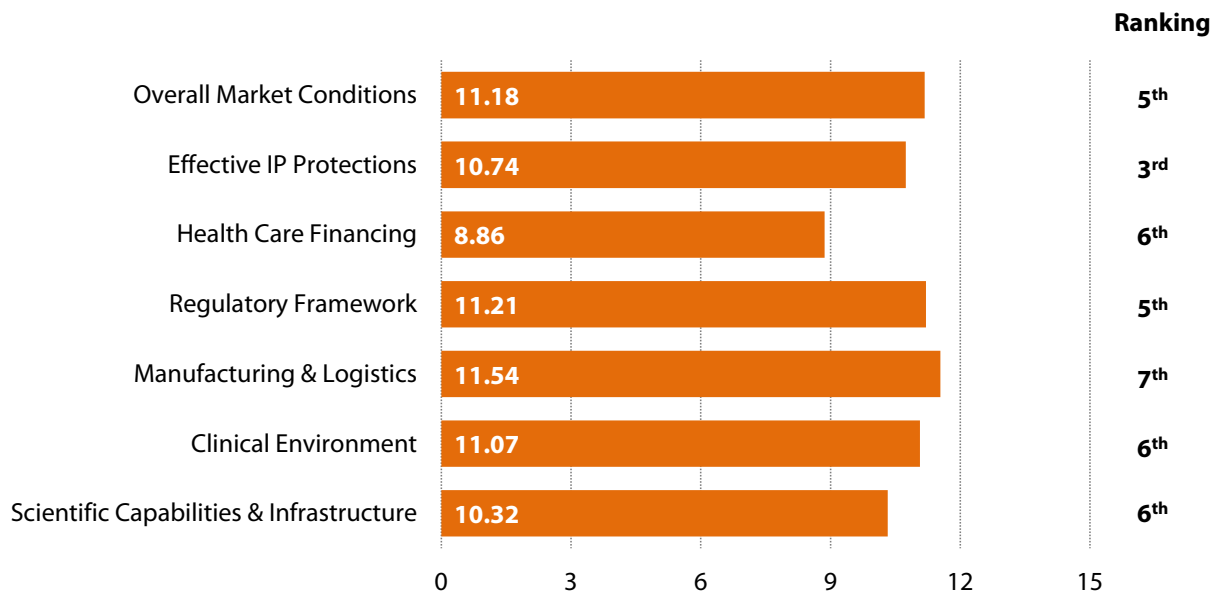


Source: Pugatch Consilium, 2015.

Notes:

1) The Biopharmaceutical Investment and Competitiveness (BCI) Survey of 2015 maps the biomedical policy ecosystem and provides perspective on the biomedical investment environment across national economies. The BCI survey is a global survey-based index of the biomedical investment attractiveness of economies, including an examination of the following major areas: ability to leverage scientific capabilities and infrastructure; state of the clinical environment, from test tube to patients; quality and efficiency of biomedical manufacturing and logistics operations; soundness and effectiveness of the biomedical regulatory framework; health care financing; and overall market and business conditions (Pugatch Consilium, 2015). Additional information about how these categories are defined and measured and how the data were collected may be found in the study by Pugatch Consilium (2015).

2) Canada's low score results from several factors, including the limited period of data exclusivity. In addition, the "Canadian standard of utility established through this expanding case law differs from international standards embodied in TRIPS and the Patent Cooperation Treaty, and from practices of patent offices in the United States and European Union. The utility test is accompanied by a heightened evidentiary burden, requiring innovators to demonstrate the effectiveness of a pharmaceutical in light of the court's subjective construed 'promise.' The test raises uncertainty as to how much information needs to be disclosed in patent applications, and discriminates against pharmaceutical patents" (GIPC, 2015: 48).

Figure 8: Biopharmaceutical Scores by Category for Canada

Source: Pugatch Consilium, 2015.

Unfortunately, this may be inadequate to truly foster a robust, innovative biopharmaceutical industry in Canada.

While Canada possesses many strengths in the life science arena—world-class talent, outstanding universities, a strong health care system, and rigorous regulatory framework—the existing gaps in the IP architecture significantly weaken Canadian competitiveness. The Canadian interpretation of the utility standard has been particularly controversial.¹⁸

¹⁸ Consider the following explanation by McDermid (2014): “The established international standard under the WTO’s Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement... is that an invention must be novel, not obvious, and ‘useful or capable of industrial application’ to be awarded a patent. However, Canadian courts, through the promise doctrine, are holding innovators to an entirely different standard. The promise doctrine makes Canada the only developed country in the world with a patent utility standard that is inconsistent with both NAFTA and TRIPS. This promise doctrine has three aspects: a process where the judge subjectively interprets the ‘promise of the patent’ from the patent application; a requirement that the promised utility either be demonstrated or be based on a ‘sound prediction’ of utility on the date of the patent application; and a requirement that evidence establishing a ‘factual basis’ and ‘sound line of reasoning’ for the predicted utility be disclosed in the original patent application. The promise doctrine causes

Figure 9: Map of the National Biopharmaceutical Environment in Canada

Key areas of strength	Scientific Capabilities & infrastructure	lowering for release of confidential business information.
<ul style="list-style-type: none"> • High quality scientific and clinical research capabilities • Regulatory standards in line with international best practices • Quality control framework for manufacturing and distribution quite strong 	<ul style="list-style-type: none"> • Scientific education viewed as of high quality, with a wide breadth of life sciences disciplines. • Weaknesses were identified in the translation and commercialization of research into products. 	Health Care Financing <ul style="list-style-type: none"> • Respondents had quite significant concerns with what was perceived as restrictive pricing of biopharmaceuticals. • Executives also regarded decision-making within the P&R system as fairly arbitrary and noted difficulty competing effectively in public procurement.
Key areas of weakness	Clinical Environment	Effective IP Protections
<ul style="list-style-type: none"> • Mediocre IP environment that deviates from international norms in patenting and enforcement • Overly restrictive and somewhat hostile P&R environment • Some delays in regulatory system • High costs and remaining gap between industry and research institutions impede reaching full R&D potential 	<ul style="list-style-type: none"> • Clinical research perceived to be generally more expensive than other developed countries. • Adherence and compliance to global clinical standards overwhelmingly seen as taking place. 	<ul style="list-style-type: none"> • IP fundamentals – biopharmaceutical IP protection, the patent system and enforcement – ranked as worst among developed countries. • Respondents highlighted the heightened patent utility requirement, noting that patent case law is beginning to deviate from norms in other developed countries.
	Manufacturing & Logistics	Overall Market Conditions
	<ul style="list-style-type: none"> • Manufacture, distribution and storage of biopharmaceuticals was overwhelming regarded as meeting the highest international standards. • Some challenges were identified with regards to the importation of APIs and release of such materials by relevant authorities. 	<ul style="list-style-type: none"> • Overall respondents found Canada to be a somewhat attractive destination for biopharmaceutical investment in the near future. • However, concerns were raised over a general lack of governmental support for the biomedical sector.
	Regulatory Framework	
	<ul style="list-style-type: none"> • Drug regulators generally viewed as having a high level of competency in market approval. • Concerns were raised regarding regulatory delays of over 1 year as well as proposed legislation al- 	

Source: Pugatch Consilium, 2015.

Notes:

1) 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 U.S. 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 manufacturers 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.

2) P&R is the abbreviation for "pricing and reimbursement." API is the abbreviation for "active pharmaceutical ingredient."

Canada's unique misinterpretation of the utility standard resulted in the revocation of 18 patents on the basis that they are 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 mechanism 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). However, the final ratification of the Comprehensive Economic and Trade Agreement (CETA), a free trade agreement between Canada and the European Union, would significantly strengthen Canada's IP environment. Notably, as a result of the CETA negotiations, Canada will move from no patent term restoration to 2 years.^{19,20} In addition, under the terms of the CETA negotiations, if an innovative firm fails in its NOC application, the patent holder and the generic challenger are entitled to equivalent and effective rights of appeal, though it remains to be seen how this will be implemented under Canadian IP legislation.²¹ Ratification would bring these changes into effect in late 2016 at the earliest.

significant uncertainty for innovators because it not only requires the innovator to 'soundly predict' how its invention will be used but also provide enough information in the patent application to prove the invention will successfully fulfill its promise" (McDermid, 2014: 1).

¹⁹ Many factors may shorten the length of the effective patent term, including requirements imposed by government regulatory authorities. For example, firms are required to obtain federal approval before marketing. Consequently, in an effort to stimulate innovation, patent restoration terms extend patent life to compensate innovators for the time lost while awaiting government approval.

²⁰ Two years for the patent restoration term is still less than the period allowed by other industrialized nations. The EU provides up to five years and requested a term of five years in the negotiations of the CETA.

²¹ Prior to CETA negotiations, if an innovative pharmaceutical firm failed in its Notice of Compliance application, a generic producer could be granted an NOC shortly thereafter and the Canadian Federal Court previously held that it would not hear any appeal by an innovator company. Conversely, should a generic lose its NOC proceeding, it retained its right to appeal.

Conclusions

In an impressive technological leap, the development of biologics is 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 both increasing value in the future and a shift by the biopharmaceutical industry toward devoting a growing proportion of research and development pipelines to biologics. Notably, several pharmaceutical firms have explicit targets ranging from 20 percent to more than 75 percent for the biologics share of their research pipelines (Meininger, 2014). 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. 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. These issues also extend to the development, production, and regulation of subsequent entry biologics.

History teaches that technology evolves faster than the legal architecture that surrounds it. The continued development of biologic medicines hinges on the intellectual property protection provided on a global scale. Patent protection and data exclusivity protections are both essential to the efficient provision of incentives that will spur the development of biologics. In particular, data exclusivity is a straightforward step that will help the law catch up to the science that brings us biologic medicines. Biologic medicines are essential to the health care advances of the future, and data exclusivity is crucial to innovative biologics. 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 with any new technology, the advent of biologic medicines brings with it a number of challenges. These areas need additional study, empirical analysis, and creative thinking. In particular, the following challenges remain:

- » What is the most effective means of protecting the intellectual property embodied in biologics? What role does data exclusivity play and for what period of time?
- » How should biologics and subsequent entry biologics be named? How important is nomenclature in developing the market and safeguarding patient health and safety?
- » How will authorities regulate pharmacovigilance²² and tracking of both biologics and SEBs? What is efficient and what will best serve patient and industry needs?
- » How much cost savings will result from subsequent entry biologics? What is the impact of different intellectual property rights regimes on this saving and how is that to be balanced with sufficient protection that will give incentives for their development?
- » If pricing and reimbursement policies are regional in nature, how do we ensure equitable access and payment?
- » What are the safest and most efficient approval pathways for subsequent entry biologics in order to ensure competition protect patient health?
- » What is the way to develop a safe and effective policy on the interchangeability and substitutability of subsequent entry biologics with their pioneer reference products?

This study provides an introduction to biologic medicines 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 a discussion of how biologics differ from traditional small molecule pharmaceuticals. It also covers the importance of precision in biologic development and manufacturing. Importantly, 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. The paper touches on the distinctions and similarities between the markets for small molecule generic drugs and non-innovator biologics and, finally, presents a description of the Canadian specifics for the biopharmaceutical industry and describes a number of areas for future work. Understanding both the

²² Pharmacovigilance, also known as drug safety, consists of data collection, the detection of adverse events, analysis, assessment, and pharmaceutical product monitoring.

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 to ensure their development, and that they are precisely developed, responsibly manufactured, and effectively brought to those who need them.

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