Intellectual Property Rights and the Promotion of Biologics, Medical Devices and Trade in Pharmaceuticals

Edited by Steven Globerman

Contents

Introduction

by Steven Globerman[1]

The aging of the population in many parts of the world is putting increased financial strain on national health care systems, as well as challenging research scientists and health care companies to develop new drugs, medical devices, and procedures to effectively and efficiently address the escalating demands of age-related diseases.

New pharmaceuticals have long been a major contributor to improving the health status of society, especially among older people (Miller and Frech, 2000; Lichtenberg, 2001). At the same time, innovation in biopharmaceuticals and medical devices is extremely risky and expensive, which contributes to a major and ongoing tension in the public policy arena between encouraging such innovation and constraining the growth of health care costs (Kleinke, 2001). This tension has been highlighted in several recent cases involving the introduction of new drugs which, while more effective than existing drugs, are also more expensive. The higher prices have drawn criticism from politicians, consumer groups, and even health care practitioners. An example is the Hepatitis C drug (Sovaldi) made by Gilead Sciences Inc. When introduced in 2014, the drug cost about US$84,000 for a patient on a standard, 12-week treatment schedule. While the drug was acknowledged to be a superior treatment to existing therapies in that it actually offered a cure for the condition, the US Senate Finance Committee demanded a justification of the pricing of the drug

[1] The author thanks Kristina Lybecker for helpful comments and suggestions.

and highlighted the lower prices charged for the drug in other countries (Web MD News Archive, 2014).[2]

Where a new drug or medical device promises cost savings over existing alternatives, there should presumably be little conflict surrounding the willingness of the health care system to pay for the innovation. However, when the innovation threatens to increase the overall costs of the health care system, the evaluation is clearly more complex and requires weighing the benefits against the costs of innovation.

An obvious goal of health care systems is to promote the development and use of new drugs and devices that promise net social benefits, i.e., improvements in longevity and quality of life that outweigh the associated costs of the innovations. Laws and regulations comprising the intellectual property (IP) regime are long-standing instruments of public policy to condition incentives to innovate. They are particularly important instruments in the context of innovation in the pharmaceutical sector according to surveys (Cohen, 2010). Yet tremendous controversy surrounds the issue of whether strengthening or weakening the legal IP regime would improve social welfare. Furthermore, and unsurprisingly, opinions on this issue vary across national health care regimes as evidenced by differences in IP protection afforded pharmaceutical and medical device companies operating in different countries.

The purpose of this conference volume[3] is to bring additional insight and clarity into the debate surrounding IP protection for new drugs and medical devices. In particular, the three papers in this volume highlight aspects of the economic, technological, and political environments that are directly or indirectly influencing the net social benefits of strengthening the IP regime for new drugs and medical devices. The next section of this introductory chapter will briefly review the main themes of the three conference papers, as well as the broad trade-off between innovation and affordable access to new drugs and medical devices that has traditionally informed the debate about IP protection for these industrial sectors.

[2] Sovaldi also promises fewer side effects and greater adherence rates. Recent controversy also surrounds new cholesterol drugs approved for those who cannot tolerate or benefit from existing statin drugs (see Szabo, 2016).

[3] Earlier versions of the papers in this book were presented at a private Fraser Institute conference that focused on intellectual property in the health care sector. The conference was held at the Sheraton Wall Centre in Vancouver on Friday, September 18th, 2015.

The IP protection "trade-off"

As noted above, surveys and related evidence identify IP protection, particularly strong and effective patent protection, as being an important instrument for promoting innovation in the biopharmaceutical sector. In her chapter in this book, Kristina M. Lybecker discusses the underlying theoretical justifications for the importance of patent protection to innovation, particularly for new biologic drugs. Patent protection extended to new drugs and medical devices will result in higher prices for those drugs and devices than would be the case if such patent protection did not exist, at least in the short run over the effective life of the patent. The higher resulting prices create stronger incentives for firms to innovate. Indeed, if rivals could appropriate the knowledge embodied in new drugs without compensating the innovator, there would be no incentive to assume the costs and risks of innovating. At the same time, higher prices increase the financial burden that governments, insurers, and patients must bear to gain access to new drugs and devices. The challenge for policymakers, as discussed in detail by Christopher Sands in his chapter, is to balance the incentives for innovation against the financial burdens that may compromise patients' access to new drugs.

The circumstances surrounding the assumed trade-off between the research and development benefits of a patent system and the welfare and output lost through patent monopolies and reduced price competition, as it is characterized by Tomas Philipson in his contribution to this volume, will differ across countries.[4] Hence, one would expect countries to differ in their IP regimes, particularly with regard to the patenting of pharmaceuticals. In particular, developing countries such as India have been keen to boost their own generic pharmaceutical firms, while suppressing prices of imported drugs and even refusing to grant patents for some innovations. The result is that IP protection in developing countries has been weaker than in developed countries with a resulting conflict between the governments of developing and developed countries in venues such as multilateral and regional trade negotiations. Christopher Sands discusses this conflict in detail in his chapter and also notes that differences of opinion about "appropriate" IP regimes also exist across developed countries. In this regard, both Sands and Lybecker identify Canada as providing significantly weaker IP protection to biopharmaceutical innovators relative to most other developed countries.

Given the limits on our state of knowledge, it is impossible to identify the "optimal" amount of IP protection for any national regime, let

[4] The trade-off is also often characterized as one between static and dynamic efficiency.

alone identify a harmonized (across nations) regime that would maximize some world "welfare function." However, each of the contributions to this book highlight conditions surrounding the biopharmaceutical and medical device sectors which make it more likely, rather than less likely, that the international IP regime encourages too little innovation relative to post-patent price competition. Put slightly differently, the conference papers suggest some reasons why the benefits of stronger IP protection may have been understated in the past relative to the benefits of weakening patent monopolies.

In his chapter, Tomas Philipson discusses a fundamental public goods problem associated with the development of new drugs and medical devices. Specifically, the expected profits to companies from innovating are a positive function of worldwide spending on drugs and medical devices. At the same time, individual countries have incentives to limit their spending on patented drugs and "free-ride" on the spending of other countries. Spending can be limited, for example, by providing weak IP protection for patented drugs and medical devices developed elsewhere. The free-riding incentive is particularly strong for emerging economies such as India, China, and South Africa that spend relatively little on new drugs and devices. In such cases, reductions in spending, on the margin, will have a relatively small impact on overall worldwide spending and, therefore, on overall worldwide innovation. An implication is that national IP regimes will generally be weaker than they "should be" from a global welfare-maximizing standpoint if countries collectively engage in free-riding, other things constant, since the overall spending impact of collective free-riding will be substantial.

Kristina Lybecker's chapter provides a detailed discussion of the biologics revolution whereby large-molecule, protein-based drugs made using living organisms are increasing in importance relative to traditional, small-molecule drugs made through chemical processes. If anything, this revolution argues in favour of strengthening IP regimes for new drugs, as well as developing new IP mechanisms to encourage innovation in this field. In particular, the tremendous costs of bringing a new biologic medicine to market makes the protection granted to innovators through IP rights disproportionately important for the biopharmaceutical industry. Lybecker estimates that on average, biologics currently cost 22 times that of non-biologic drugs to develop.

Lybecker also highlights the anticipated smaller gains to shortening the period of IP protection for patented biologics. For one thing, it is relatively expensive to develop subsequent entry biologics (SEBs) as compared to developing generic versions of small-molecule compounds. Hence, the anticipated static efficiency gains from reducing the effective period of

monopoly IP protection for new biologics are likely much smaller than the static efficiency gains from allowing the earlier introduction of generic pharmaceutical drugs. For another, it is much more difficult to ensure the safety and efficacy of SEBs compared to ensuring the safety and efficacy of traditional generic pharmaceuticals. Hence, the risks and potential costs of the "premature" introduction of SEBs are higher than for the early introduction of generic pharmaceutical drugs.

Philipson also identifies a feature of the IP process that likely reduces the static efficiency gains from shortening the period of monopoly status for a drug through weakening the IP regime. Namely, patent expirations decrease the private returns to marketing which disappear when goods are sold at marginal cost. As a result, patent expirations may actually result in reduced output of the formerly patented drugs if they decrease marketing effort by enough to offset the impact of price reductions. Philipson finds that for non-advertised drugs, quantity rises fairly steadily after patent expirations; however, for advertised drugs, quantity appears flat after patent expiration. On balance, patent expiration does lead to lower costs of the previously patented drug for consumers; however, the reduction in advertising reduces the total gain to consumers from patent expiration by a substantial amount.

Finally, Sands also discusses some phenomena that are effectively reducing the protection afforded drug developers through IP regimes. He notes that advanced manufacturing and automation are making it possible to quickly and cheaply design (or reverse engineer), mass produce, and distribute new products to market worldwide very quickly. This places pressure on IP regimes from counterfeiters, imitators, and others who can exploit gaps in IP rights or regulatory approval to capture market share that would otherwise be captured by the patent holders. Any such appropriation of the "required" returns to the original innovator would discourage innovation, at the margin, and especially discourage the investments required for expensive "breakthrough" innovations.

Conclusions

The papers presented in this volume provide some new perspectives on the long-standing debate about the efficient IP regime for biopharmaceuticals and medical devices. On balance, they suggest that a strengthening of IP protection is likely to improve social welfare by encouraging innovation in the biopharmaceutical and medical device sectors, especially as current and emerging features of those sectors, particularly for biopharmaceuticals,

are characterized by attributes that strengthen the linkages between R&D benefits and IP protection and weaken the expected static benefits of patent expirations.

The free-rider problem described by Philipson, along with an unequal (across nations) distribution of the benefits and costs of IP protection ensure that IP issues will be a future source of conflict among countries, as they have been in the past. In this regard, Canada's IP regime has been a source of friction with other developed countries, as both Sands and Lybecker detail.

The way forward for drug companies is both fraught and unclear. The Trans-Pacific Partnership (TPP) provides for a multilateral strengthening of IP protections for biopharmaceuticals. However, as of this writing, the outlook for the implementation of the TPP is not favourable given the negative positions on it taken by the two US presidential candidates in the 2016 election and by a Congress that seems disinclined to approve major new free trade deals. The free trade deal negotiated between Canada and the European Union, which strengthens Canadian IP provisions, is taking a long time for EU approval, and this approval process may be further delayed, if not undone, by Great Britain's decision to leave the EU. Likewise, any further movement toward a free trade agreement between the US and the EU will likely be on hold until the terms of Britain's exit from the EU are negotiated. In short, coordinated efforts to implement stronger IP regimes through multilateral or regional trade agreements seem unlikely over the foreseeable future.

The continued growth of emerging market economies, particularly China and India, should increase demand for biopharmaceuticals and medical devices in those economies. Other things constant, this should augment the worldwide returns to R&D efforts for drug and device companies, thereby encouraging innovation. However, as Philipson notes, as the share of total spending on drugs and medical devices by emerging markets grows, the incentives of the US and other developed economies to contribute to those worldwide returns diminishes. The net impact on the incentives for companies to innovate is therefore, as Philipson puts it, a horse race.

A movement on the part of national health care systems in developed countries to implement cost-effectiveness criteria to guide decisions about the adoption and payment for new and existing technologies might also be a significant source of bias against the introduction of new drugs and medical devices, as Philipson explains. Growing political pressure for government-price-setting authorities to limit payments for new drugs represents yet another challenge to the innovation process. As well, significant regulatory reforms will be needed in the United States and else-

where if the prices of new drugs are going to be tied to the usefulness of the clinical setting in which they are prescribed (Gottlieb and Patel, 2016).[5]

In an environment where much of the public objects to high drug prices and sees drug companies as villains, Sands advises those companies to focus on promoting government policies that would lower the overall costs of drug development. These include shortening the length of time it takes for patent and regulatory approvals and providing for simultaneous and continuous approvals across multiple national markets through government regulatory cooperation. Employing big data analytics to track biological performance and to share data among regulators could also reduce the costs that drug firms incur to receive regulatory approvals as well as expedite value-based pricing for new drugs.

In short, emerging technology holds great promise for life-enhancing and life-extending new drugs and medical devices; however, laws and regulations comprising the IP regime for drugs and medical devices are arguably biased in favour of post-patent price competition. Ultimately, government policies affecting the innovation environment will depend upon the value that societies place on new life-enhancing and life-extending drugs. In the meantime, the public is not well served by political rhetoric that obscures the need for companies to be rewarded for the substantial costs and risks they incur when undertaking innovation.

References

Cohen, W. (2010). Fifty Years of Empirical Studies of Innovative Activity and Performance. In Bronwyn Hall and Nathan Rosenberg (eds.). *Handbook of the Economics of Innovation* (Elsevier): 129–213.

Gottlieb, S. (2016, August 20-21). How Obama's FDA Keeps Generic Drugs off the Market. *Wall Street Journal*: A13.

Gottlieb, S., and K. Patel (2016, July 11). A Fair Plan for Fairer Drug Prices. *Health Affairs Blog.* <http://healthaffairs.org/blog/2016/07/11/a-fair-plan-for-fairer-drug-prices/>, as of August 23, 2016.

Kleinke, J.D. (2001). The Price of Progress: Prescription Drugs in the Health Care Market. *Health Affairs* 20, 5: 43–60.

[5] Gottlieb (2016) also highlights the adverse impact of increasing regulatory costs on the rate of introduction of generic drugs.

Lichtenberg, F. (2001). Are the Benefits of Newer Drugs Worth Their Costs? Evidence from the 1996 MEPS. *Health Affairs* 20, 5: 241–251.

Lybecker, K. (2016). The Biologics Revolution in the Production of Drugs. *Intellectual Property Rights and the Promotion of Biologics, Medical Devices, and Trade in Pharmaceuticals.* The Fraser Institute.

Miller, R.D., and H.E. Frech (2000). Is There a Link Between Pharmaceutical Consumption and Improved Health in OECD Countries? *Pharmacoeconomics* 18, Suppl 1: 33–45.

Philipson, T. (2016). Unique Aspects of Patents for Medical Innovation: Recent Research Results. *Intellectual Property Rights and the Promotion of Biologics, Medical Devices, and Trade in Pharmaceuticals.* The Fraser Institute.

Sands, C. (2016). The Calculus of Convergence: Intellectual Property Rights for Pharmaceuticals and the Global Trade Agenda. *Intellectual Property Rights and the Promotion of Biologics, Medical Devices, and Trade in Pharmaceuticals.* The Fraser Institute.

Szabo, L. (2016, August 17). Price of Cholesterol Drugs May Get Painful. *USA Today:* 1.

Web MD News Archive (2014, July 14). High Cost of Hepatitis C Drug Sovaldi Investigated. WebMD. <http://www.webmd.com/hepatitis/news/20140714/high-cost-hepatitis-c-drug-sovaldi-investigated>, as of August 23, 2016.

The Biologics Revolution in the Production of Drugs

By Kristina Lybecker

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

[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).

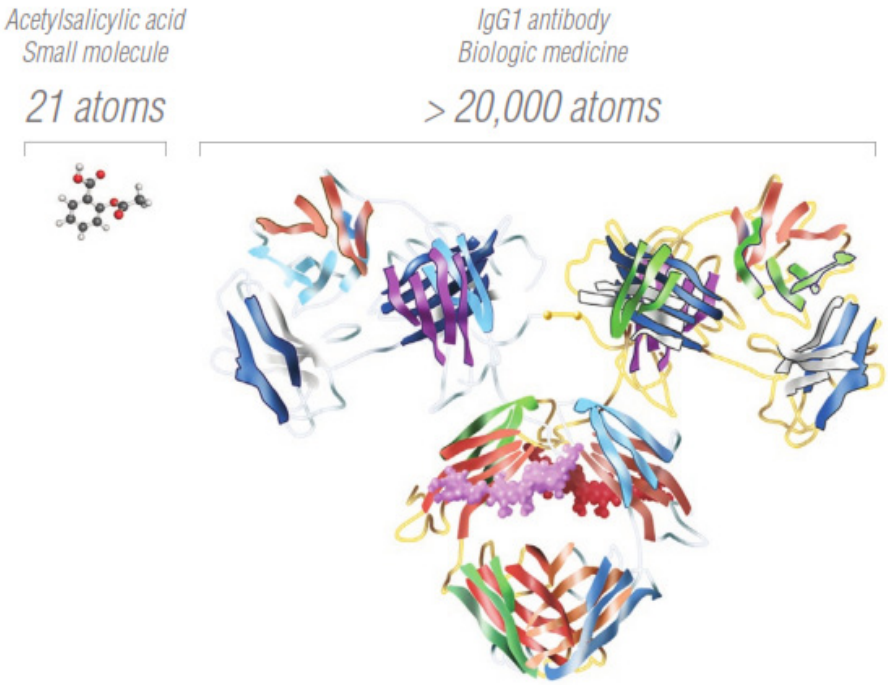
on, the focus of biotechnology shifted from primarily food production to the development of medicines. By the early 1940s, humanity was benefitting from the mass production of antibiotics, and in the early 1950s, the structure of DNA was discovered, laying the groundwork for modern biotech advances in medicine. Nevertheless, a consensus on the meaning of biotechnology was not reached until the United Nations and World Health Organization accepted the Convention on Biological Diversity of 1992. 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).

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.

Figure 1: Comparison of Small Molecule Pharmaceuticals and Biologics



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

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 contrasts the complexity and structure of a conventional small molecule drug, with a biologic.

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 replication (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.

[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.

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).

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.

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

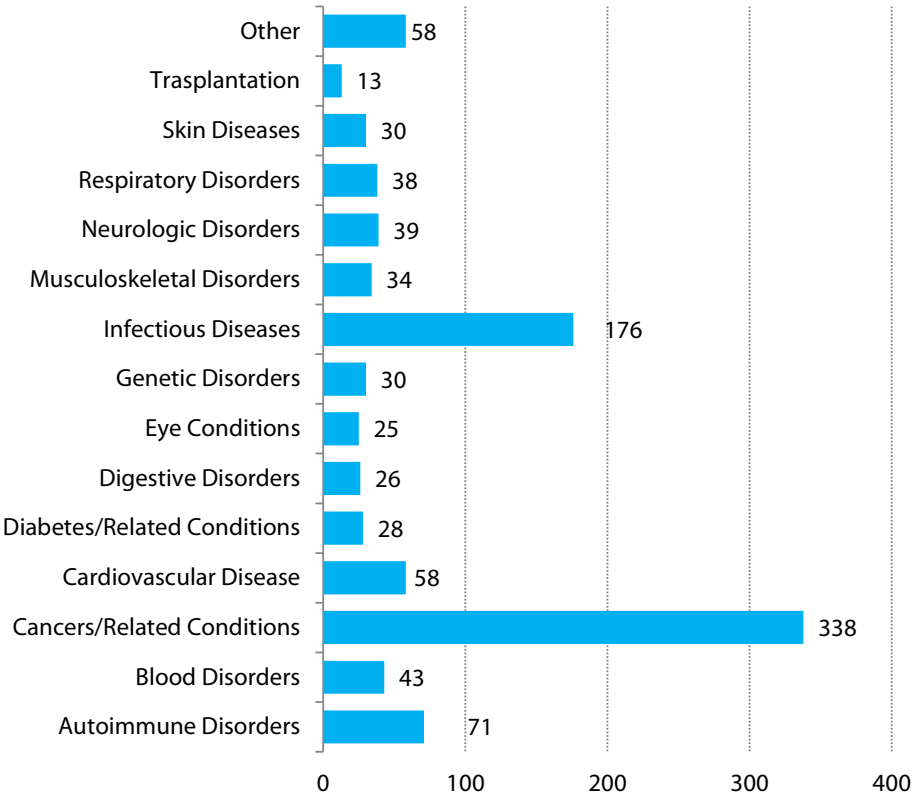
To date, more than 250 biologic therapies and vaccines have transformed the lives of hundreds of millions of patients (BIO, 2015). In the United States, more than 900 biologics are currently in development for more than 100 diseases (*The Economist*, 2015). Figure 2 describes these efforts by therapeutic 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

[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.

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).

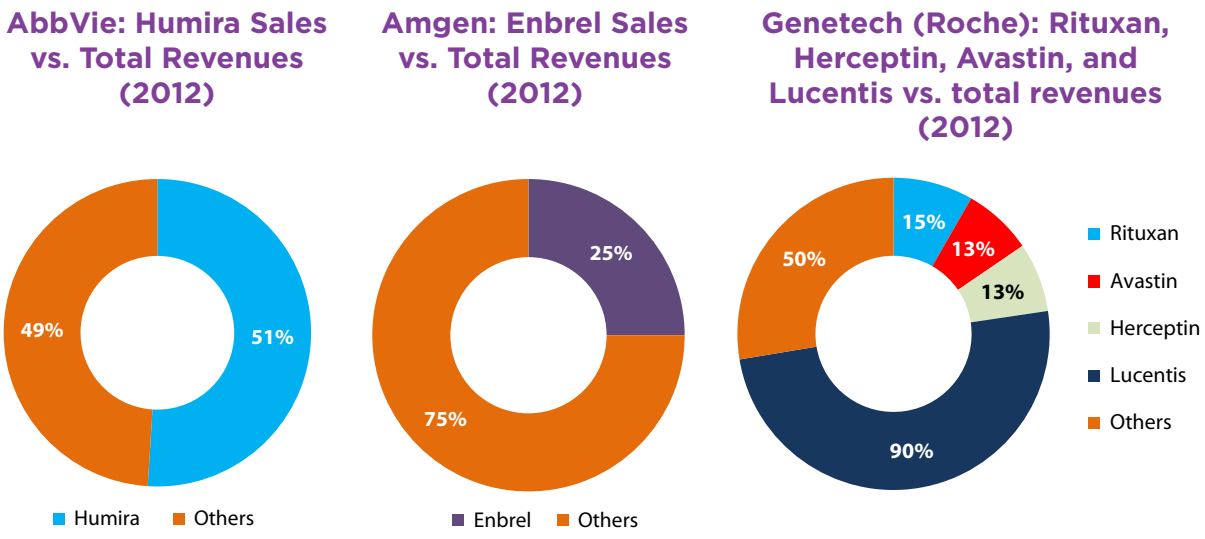
Current estimates suggest that biologics provided close to 22 percent of the sales of large pharmaceutical firms in 2013, and expectations are that this will rise to 32 percent by 2023 (The Economist, 2015). Moreover, in 2011, global spending on biologic medicines increased 7 percent, compared to a mere 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 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 depicts the share revenues generated by biologics for three industry leaders, AbbVie, Amgen, and Genetech, in 2012.

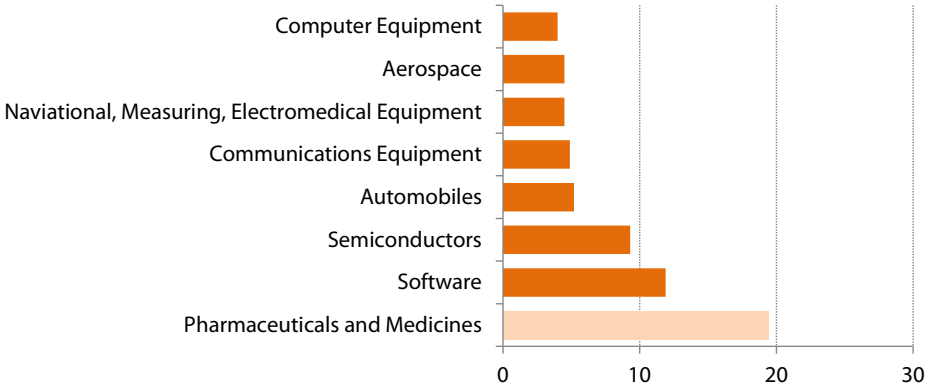
While currently a growing source of revenue, the market exclusivity enjoyed by many of these products will erode as patents expire and competing products enter the market. In 2016, biologics with US sales totaling $60 billion will lose patent protection in the US market (Silverman, 2015). Beyond patent 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 de-

Figure 3: The Importance of Biologics



Source: White, 2014.

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



Source: PhRMA, 2013a.

generation. 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 (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 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

[5] This includes producers of both biologics and small molecules.

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).

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[6] 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

[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.

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 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]

[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.

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 $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

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).

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 trial results.[9] This information must be protected with data exclusivity

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

[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

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 complementary 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 in-

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.

novator'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

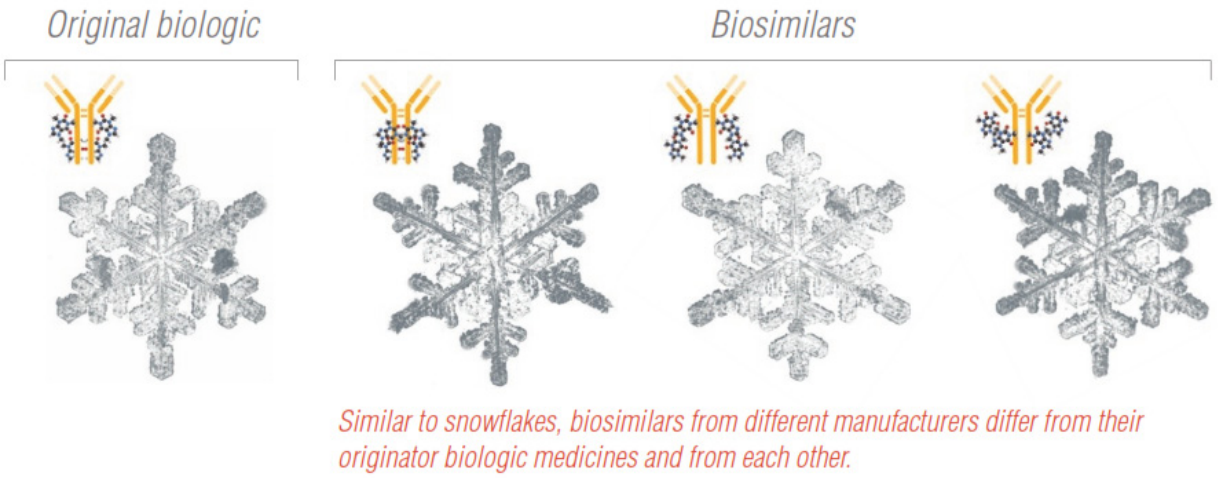
As the market for biologic medicines matures, generic versions—properly known in Canada as subsequent entry biologics or SEBs—will enter the market. The creation of subsequent entry biologics is considerably different from the creation of generic versions of traditional small molecule drugs. Similarly,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

Figure 6: Illustrating the Differences between Original Biologics and Biosimilars



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

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 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 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

Table 2: Characteristics of Small Molecule Pharmaceuticals vs. Biologics

	Small Molecule Generics	Subsequent Entry Biologics
Product Characteristics	Small molecules	Large, complex molecules
	Often very stable	Stability requires special handling
	Easy to fully characterize	Hard to characterize
	Mostly without a devise	Device is often a key differentiator
Production	Chemical Synthesis	Produced in living organisms
	Simple	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	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*
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
		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, GabI, 2014).

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 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 be 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

[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.

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 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.

[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 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).

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. 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).

[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).

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 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%" (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 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).

Canadian specifics

Canada's protection of intellectual property in the life sciences significantly lags behind that provided by many other industrialized nations, including

[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.

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.

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 1987[16] and 1992[17] changes to Canada's Patent Act that strengthened

[16] As described by the Parliament of Canada, the 1987changes 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 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

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.

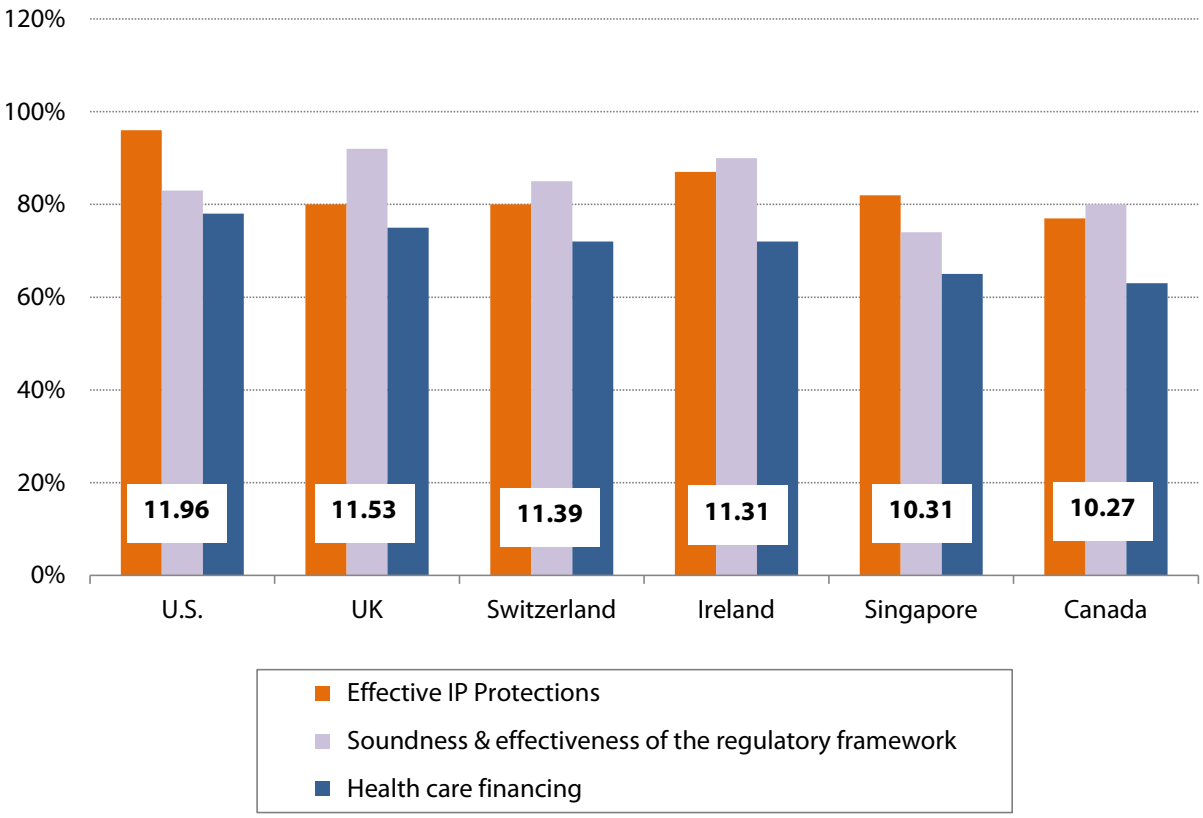
Figure 8 provides more specifics on the Canadian market, considering seven factors of critical importance to the biopharmaceutical industry. Figure 9 presents additional details on each of the areas examined in Figure 8. Canada ranks between 3rd and 7th across each of these measures. Unfortunately, this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

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).

[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

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.

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

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 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).

Figure 9: Map of the National Biopharmaceutical Environment in Canada

Key areas of strength

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

Key areas of weakness

- 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

Scientific Capabilities & infrastructure

- 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.

Clinical Environment

- Clinical research perceived to be generally more expensive than other developed countries.
- Adherence and compliance to global clinical standards overwhelmingly seen as taking place.

Manuracturing & Logistics

- 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.

Regulatory Framework

- Drug regulators generally viewed as having a high level of competency in market approval.
- Concerns were raised regarding regulator y delays of over 1 year as well as proposed legislation allowing for release of confidential business information.

Health Care Financing

- 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.

Effective IP Protections

- 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.

Overall Market Conditions

- 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.

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."

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.

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).

[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.

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 incentivizes 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 effect 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?

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

- 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 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.

References

Amgen (2014). *Biologics and Biosimilars: An Overview*. Online post (March). Amgen. <http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf>, as of March 24, 2015.

Arrow, Kenneth (1962). Economic Welfare and the Allocation of Resources for Invention. In National Bureau Committee for Economic Research (ed.). *The Rate and Direction of Inventive Activity: Economic and Social Factors.* Princeton University Press: 609-626. <www.nber.org/chapters/c2144.pdf>, as of May 17, 2016.

Bayer Health Care (n.d.). Small and Large Molecules: Drugs on a Chemical and Biological Basis. *Small and Large Molecules*. Web page. <http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/>, as of May 11, 2016.

Birkett, D.J. (1994). Pharmacokinetics Made Easy 9: Non-linear Pharmacokinetics. *Australian Prescriber* 17 (April): 36-38. <http://www.australianprescriber.com/magazine/17/2/36/8>, as of May 17, 2016.

Biotechnology Industry Organization [BIO] (2013). *The Trans-Pacific Partnership and Innovation in the Bioeconomy: The Need for 12 Years of Data Protection for Biologics*. Online posting (July 18). BIO. <www.bio.org/sites/default/files/TPP%20White%20Paper%20_2_.pdf>, as of May 17, 2016.

Biotechnology Industry Organization [BIO] (2015). *What is Biotechnology?* Web page. BIO. <https://www.bio.org/what-biotechnology>, as of May 17, 2016.

Biotechnology Industry Organization [BIO] (2010a). Why is Patient Safety a Concern in the Biosimilars Debate? Web page. BIO. <http://www.bio.org/articles/why-patient-safety-concern-biosimilars-debate>, as of May 17, 2016.

Biotechnology Industry Organization [BIO] (2010b). *How do Drugs and Biologics Differ?* Web page. <https://www.bio.org/articles/how-do-drugs-and-biologics-differ>, as of May 17, 2016.

Blackwell, Tom (2015, February 5). Health Canada Halts Import of Drugs from Two Indian Factories over 'Data Integrity' Concerns. *National Post.* <http://news.nationalpost.com/news/canada/health-canada-halts-import-of-drugs-from-two-indian-factories-over-data-integrity-concerns>, as of May 17, 2016.

Busch, Alaina (2014, January 9). Biosimilar Developers Prepare for Applications in 2014, Approvals Mid Decade. *FDA Week*. <https://www.ftc.gov/es/system/files/documents/public_comments/2014/02/00019-88669.pdf>, as of May 17, 2016.

Business Roundtable (n.d.). *The Trans-Pacific Partnership Agreement: An Opportunity for America*. Business Roundtable. <http://businessroundtable.org/sites/default/files/reports/TPP%20Overview%202016.pdf>, as of May 25, 2016.

Canadian Intellectual Property Council [CIPC] (2011). *Innovation for a Better Tomorrow: Closing Canada's Intellectual Property Gap in the Pharmaceutical Sector*. Canadian Chamber of Commerce. Can be found in a

list of reports on <http://chamber.ca/advocacy/issues/intellectual-property/>, as of May 17, 2016.

Chance, Kamali (2010). The US Approval Pathway for Biosimilar Products. *Regulatory Focus*15, 10 (October): 34–36. <www.raps.org/WorkArea/DownloadAsset.aspx?id=3263>, as of May 17, 2016.

Daley, Jill, and Kristin Wall (2104, April 30). *Following the Biologic Path.* PMLive.com. <http://www.pmlive.com/pharma_news/following_the_biologic_path_563862>, as of May 17, 2016.

DiMasi, Joseph A., and Henry G. Grabowski (2007). The Costs of Biopharmaceutical R&D: Is Biotech Different? *Managerial and Decision Economics* 28.

Dolinar, Richard (2012). It's All About the Name: What is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapies? *FDLI's Food and Drug Policy Forum* 2, 22, (November 28). <http://safebiologics.org/pdf/fdli-asbm-its-all-about-the-name.pdf>, as of June 12, 2014.

Douglas, Kristin, and Célia Jutras (2008, October 6). *Patent Protection for Pharmaceutical Products in Canada—Chronology of Significant Events*. Number PRB 99—46E. Parliament of Canada, Law and Government Division. <http://www.parl.gc.ca/content/lop/researchpublications/prb9946-e.htm>, as of May 17, 2016.

Economics and Statistics Administration and the United States Patent and Trademark Office (2012). *Intellectual Property and the U.S. Economy: Industries in Focus* (March). US Department of Commerce. <http://www.uspto.gov/news/publications/IP_Report_March_2012.pdf>, as of May 17, 2016.

The Economist (2015, January 3). Going Large. *The Economist* online edition. <http://www.economist.com/news/business/21637387-wave-new-medicines-known-biologics-will-be-good-drugmakers-may-not-be-so-good>, as of May 21, 2016.

Eguale, Tewodros, David L. Buckeridge, Nancy E. Winslade, Andrea Benedetti, James A. Hanley, and Robyn Tamblyn (2012). Drug, Patient, and Physician Characteristics Associated with Off-label Prescribing in Primary Care. *Archive of Internal Medicine 172*, 10: 781–788. <http://archinte.jamanetwork.com/article.aspx?articleid=1149634>, as of May 17, 2016.

Express Scripts (2014). *The Need for U.S. Biosimilars*. Infographic. Express Scripts. Available at: <https://lab.express-scripts.com/~/media/pdfs/infographic_need_for_biosimilars.ashx>, *as of May 17, 2016.*

Falvey, Rod, Neil Foster, and Olga Memedovic (2006). *The Role of Intellectual Property Rights in Technology Transfer and Economic Growth: Theory and Evidence.* Working Paper. United Nations Industrial Development Organization [UNIDO]. <http://www.unido.org/fileadmin/user_media/Publications/Research_and_statistics/Branch_publications/Research_and_Policy/Files/Working_Papers/2006/WPjuly2006%20IPR_rights_in_technology_transfer.pdf>, as of May 17, 2016.

First Word (2010). *Biosimilars: Surveying the Market Landscape. A First Word Dossier Market Intelligence Report*. Slide presentation. First Word (October). <http://www.slideshare.net/driceman/biosimilarsreport>, as of May 17, 2016.

Fuhr, Joseph P., Amitabh Chandra, John Romley, Tiffany Shih, Suepattra G. May, and Jacqueline Vanderpuye-Orgle. (2015). Product Naming, Pricing, and Market Uptake of Biosimilars. *Generics and Biosimilars Initiative Journal* 4, 2 (May 19): 64–71. <http://gabi-journal.net/product-naming-pricing-and-market-uptake-of-biosimilars.html >, as of May 17, 2016.

Gaffney, Alexander (2014, August 4). *FDA Stance on Naming Biosimilars Reportedly Finished, Awaiting Government Approval*. Web page. Regulatory Affairs Professionals Society. <http://www.raps.org/Regulatory-Focus/News/2014/08/04/19939/FDA-Stance-on-Naming-Biosimilars-Reportedly-Finished-Awaiting-Government-Approval/>, as of May 17, 2016.

Garde, Damian (2014, May 14). *FDA Breaks Silence on Biosimilars with Long-awaited Proposal*. Web page. FierceBiotech. <http://www.fiercebiotech.com/story/fda-breaks-silence-biosimilars-long-awaited-proposal/2014-05-14>, as of May 17, 2016.

Generics and Biosimilars Initiative [GaBI] (2015, April 7). *Switching and Extrapolation of Subsequent Entry Biologics in Canada*. Web page. Generics and Biosimilars Initiative. <http://gabi-journal.net/news/switching-and-extrapolation-of-subsequent-entry-biologics-in-canada>, as of May 18, 2016.

Generics and Biosimilars Initiative [GaBI] (2014, December 5). *Subsequent Entry Biologics Approved in Canada*. Web page. Generics and Biosimilars Initiative. <http://www.gabionline.net/Biosimilars/General/Subsequent-entry-biologics-approved-in-Canada>, as of May 18, 2016.

Generic Pharmaceutical Association [GPhA] (2016). *Biosimilars*. Web page. Generic Pharmaceutical Association. <http://www.gphaonline.org/issues/biosimilars>, as of May 18, 2016.

Getz, K.A., R.A. Campo, and K.I. Kaitin (2011). Variability in Protocol Design Complexity by Phase and Therapeutic Area. *Drug Information Journal* 45, 4: 413–420.

Global Intellectual Property Center [GIPC] (2015). *Measuring Momentum – The GIPC International IP Index.* Global Intellectual Property Center. <http://www.theglobalipcenter.com/measuring-momentum-the-gipc-international-ip-index/>, as of May 18, 2016.

Global Intellectual Property Center [GIPC] (2015). *Unlimited Potential: GIPC International IP Index*, 3rd edition (February). Global Intellectual Property Center. <http://www.theglobalipcenter.com/wp-content/themes/gipc/map-index/assets/pdf/Index_Map_Index_3rdEdition.pdf>, as of May 18, 2016.

Goad, Benjamin (2013, October 23). AARP Warns Trade Deal Could Lock in High Drug Prices. *The Hill.* <http://thehill.com/blogs/regwatch/healthcare/330199-trade-agreement-could-lock-in-high-drug-prices-aarp-warns>, as of May 18, 2016.

Grabowski, Henry, Genia Long, and Richard Mortimer (2011a). Data Exclusivity for Biologics. *Nature Reviews: Drug Discovery* 10 (January): 15-25. <http://www.nature.com/nrd/journal/v10/n1/suppinfo/nrd3277.html>, as of May 18, 2016.

Grabowski, Henry, Genia Long, and Richard Mortimer (2011b). From the Analyst's Couch: Data Exclusivity for Biologics. *Nature Reviews: Drug Discover*. <fds.duke.edu/db/attachment/1592>, as of May 18, 2016.

Greenmeier, Larry (2008). Heparin Scare: Deaths from Tainted Blood-Thinner Spur Race for Safe Replacement. *Scientific American* (November 4). http://www.scientificamerican.com/article/heparin-scare-deaths/, as of May 18, 2016.

Grootendorst, Paul, and Livio Di Matteo (2007). The Effect of Pharmaceutical Patent Term Length on Research and Development and Drug Expenditures in Canada. *Healthcare Policy* 2, 3: 63-84.

Guildford-Blake, Roxanna, and Debbie Strickland (2008). *Guide to Biotechnology 2008*. Biotechnology Industry Organization [BIO]. <http://www.bio.org/sites/default/files/BiotechGuide2008.pdf>, as of May 18, 2016.

Health Canada (2010, July 29). *Interchangeability/Substitutability of Subsequent Entry Biologics (SEBs)*. Letter to Provincial/Territorial Drug Plans Directors. Health Canada. <http://safebiologics.org/pdf/Health-Canada-Letter.pdf>, as of January 28, 2016.

Howell, Peyton (2012, March 2). How Much Cheaper Will Biosimilars Be? Web page. *FiercePharma.com*. <http://www.fiercepharma.com/story/how-much-cheaper-will-biosimilars-be/2012-03-02>, as of May 18, 2016.

IMS Health (2013). A Growing Share of All Medicines are Biologic, with Biosimilars and Non-original Biologic (NOB) Products Now Taking a Small Share of the Total Market. *Global Spending on Medicines*. Web page. <https://www.imshealth.com/files/web/IMSH%20Institute/Reports/The_Global_Use_of_Medicines_2017/global%20use%20of%20med%202017%20right6%20Biologics_Market.pdf>, as of May 18, 2016.

Jones, Alan Wayne (2011). Early Drug Discovery and the Rise of Pharmaceutical Chemistry. *Drug Testing and Analysis* 3, 6 (June): 337–344.

Kambhammettu S. (2008). *The European Biosimilars Market: Trends and Key Success Factors*. Scicast Special Reports (October 27).

Kazmin, Amy, and Andrew Ward (2015, August 5). Generic Drugs Ban Prompts India to Freeze EU Trade Talks. *Financial Times*. <http://www.ft.com/cms/s/0/4ded8ca4-3b8a-11e5-bbd1-b37bc06f590c.html#axzz3yZ3Zs1Ta>, as of May 18, 2016.

Kim, Yee Kyoung, Keun Lee, Walter G. Park, and Kineung Choo (2012). Appropriate Intellectual Property Protection and Economic Growth in Countries at Different Levels of Development. *Research Policy* 41, 2 (March): 358–375.

Klein, Agnes, and Jian Wang (2013). *Diversity of Approaches to the Interchangeability and Substitutability of Biosimilars*. Presentation (November). Health Canada. <http://www.slideshare.net/IFPMA/19-agnes-klein-health-canada>, as of May 18, 2016.

LaMattina, John (2013, June 17). BCG weighs in on First-In-Class vs. Best-In-Class Drugs—How Valuable Is Their Advice? *Forbes*. <http://www.forbes.com/sites/johnlamattina/2013/06/17/bcg-weighs-in-on-first-in-class-vs-best-in-class-drugs-how-valuable-is-their-advice/>, as of May 18, 2016.

Ledford, Heidi (2015). First Biosimilar Drug Set To Enter US Market. *Nature* 517 (January 15): 253-254. <http://www.nature.com/news/first-biosimilar-drug-set-to-enter-us-market-1.16709>, as of May 18, 2016.

Loney, Michael (2014, April 18). Canada IP Criticism. *Managing Intellectual Property*. Blog post. <http://www.managingip.com/Blog/3332416/Canada-IP-criticism-Megaupload-lawsuits-Tennessee-troll-reform-Scotch-trade-mark-Jay-Z-rulingthe-week.html>, as of May 21, 2016.

Lybecker, Kristina M. (2014). Essay: When Patents Aren't Enough: Why Biologics Necessitate Data Exclusivity Protection. *William Mitchell Law Review* 40, 4: 1427–1442. <http://open.wmitchell.edu/cgi/viewcontent.cgi?article=1590&context=wmlr>, as of May 21, 2016.

McCook, Alison (2005). Manufacturing on a Grand Scale. *The Scientist* (February 14). <http://www.the-scientist.com/?articles.view/articleNo/16229/title/Manufacturing-on-a-Grand-Scale/>, as of May 21, 2016.

McDermid, John (2014, June 11). A NAFTA Challenge to Canada's Patent Utility Doctrine is Necessary. Blog post. *IPWatchDog*. <http://www.ipwatchdog.com/2014/06/11/a-nafta-challenge-to-canadas-patent-utility-doctrine-is-necessary/id=49994/>, as of May 21, 2016.

Meininger, David (2014). IP Policy Forum: The Increasing Importance of Biologics-Based Drugs in Pharmaceutical Pipelines. *Marquette Intellectual Property Law Review*18, 1: 19–20. <http://scholarship.law.marquette.edu/cgi/viewcontent.cgi?article=1251&context=iplr>, as of May 21, 2016.

Mulcahy, Andrew W., Zachary Predmore, and Soeren Mattke (2014). *The Cost Savings Potential of Biosimilar Drugs in the United States*. Perspective PE-127-SANI. Rand Corporation. <http://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf>, as of May 21, 2016.

Park, W.G. (2008). International Patent Protection: 1960-2005. *Research Policy* 37: 761–766.

Petersen, Bert, and Peter J. Pitts (2014, June 6). Guest Commentary: AMA Should Support Distinguishable Names for Biosimilars. *Modern Healthcare*. <http://www.modernhealthcare.com/article/20140606/NEWS/306069934?template=print>, as of May 21, 2016.

Pham, N.D. (2012, May 25). IP Creates Jobs for America. Blog post. Global Intellectual Property Center, US Chamber of Commerce. <http://www.theglobalipcenter.com/ip-creates-jobs-america/>, as of May 21, 2016.

PhRMA [Pharmaceutical Research and Manufacturers of America] (2013a). *Chart Pack: Biopharmaceuticals in Perspective* (Spring). <http://www.slideshare.net/PhRMA/phrma-chart-pack-april-2013?related=1>, as of May 21, 2016.

PhRMA [Pharmaceutical Research and Manufacturers of America] (2013b). *Medicines in Development: Biologics*. 2013 Report. <http://www.phrma.org/sites/default/files/pdf/biologics2013.pdf>, as of May 21, 2016.

Pugatch, Meir, David Torstensson, and Rachel Chu (2012). *Taking Stock: How Global Biotechnology Benefits from Intellectual Property Rights* (June). Pugatch Consilium. <https://www.bio.org/sites/default/files/Pugatch%20Consilium%20-%20Taking%20Stock%20Final%20Report%20%282%29.pdf>, as of May 21, 2016.

Pugatch Consilium (2015). *Measuring the Global Biomedical Pulse: The Biopharmaceutical Investment and Competitiveness (BCI) Survey—2015*. Pugatch Consilium. <http://www.pugatch-consilium.com/reports/BCI%202015%20-%20Measuring%20the%20Biomedical%20Pulse.pdf>, as of May 21, 2016.

Rawson, Nigel S.B. (2015). *Including Off-label Drug Indications in HTA Jeopardizes Patient Health and Discourages Innovation.* Canadian Health Policy. <http://www.canadianhealthpolicy.com/products/including-off-label-drug-indications-in-hta-jeopardizes-patient-health-and-discourages-innovation.html>, as of May 21, 2016.

Richardson, Elizabeth (2013, October 10). *Biosimilars*. Health Policy Brief. Health Affairs. <http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=100>, as of May 21, 2016.

Rudmann, Daniel G. (2012). On-target and Off-target-based Toxicologic Effects. *Toxicology Pathology* 41: 310–314. <http://tpx.sagepub.com/content/41/2/310.full.pdf+html>, as of May 21, 2016.

Sandoz (n.d). *Why Biologics Matter: Biologics Contributing to Rising Healthcare Costs*. Blog Post. Sandoz. <http://www.sandoz-biosimilars.com/biosimilars2/why_biologics_matter.shtml#>, as of March 12, 2014.

Sarpatwari, Ameet, Jerry Avorn, and Aaron S. Kesselheim (2015, May 6). Progress and Hurdles for Follow-on Biologics. *New England Journal of Medicine.* <http://www.nejm.org/doi/full/10.1056/NEJMp1504672>, as of May 21, 2016.

Schofield, Ian (2014). Biosimilars take the Stage as Regulatory Debate Goes Global. *Scrip Regulatory Affairs* (September). <http://marketing.scripintelligence.com/wp-content/uploads/sites/11/2014/09/Biosimilars-take-the-stage.pdf>, as of May 25, 2016.

Silverman, Ed (2014, August 1). What's in a Name? WHO Issues Proposal for Biosimilar Names. *Wall Street Journal*, online edition. <http://blogs.wsj.com/pharmalot/2014/08/01/whats-in-a-name-who-issues-proposal-for-biosimilar-names/>, as of May 21, 2016.

Silverman, Ed. (2015, June 12). What's in a Name? Contentious Fight over Biosimilars Coming to a Head. *Wall Street Journal*, online edition. <http://blogs.wsj.com/pharmalot/2015/06/12/whats-in-a-name-contentious-fight-over-biosimilars-coming-to-a-head/>, as of May 21, 2016.

Stroud, Jonathan (2013). *Power without a Patent: Twelve-year Biologics Data Exclusivity Period and a Totality-of-the-evidence Standard for Biosimilarity*. Second International Conference and Exhibition on Biowaivers and Biosimilars, September 23-25, 2013, Raleigh, NC. <http://www.omicsonline.org/abstract/power-without-a-patent-twelve-year-biologics-data-exclusivity-period-a-totality-of-the-evidence-standard-for-biosimilarity/>, as of May 25, 2016.

Team, Trefis (2015, March 24). What Does Recent Biosimilar Approval by the FDA Mean? *Forbes*. <http://www.forbes.com/sites/greatspeculations/2015/03/24/what-does-recent-biosimilar-approval-by-the-fda-mean/#344bc7ce4358>, as of May 17, 2016.

Thimmaraju, Phani Kishore, R. Rakshambikai, Raheem Farista, Karthaveerya Juluru (2015, January 6). Legislations on Biosimilar Interchangeability in the US and EU–Developments Far from Visibility. Web page. Generics and Biosimilars Initiative [GaBI]. <http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility>, as of May 17, 2016.

United Nations (1992). *Chapter 2: The Convention on Biological Diversity*. United Nations. <https://www.cbd.int/gbo1/chap-02.shtml>, as of May 21, 2016.

United States Food and Drug Administration [US FDA] (2015, July 7). *Frequently Asked Questions about Therapeutic Biological Products*. Web page. US FDA. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm>, as of May 25, 2016.

United States Food and Drug Administration [US FDA] (2016, May 10). *Information on Biosimilars*. Web page. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>, as of May 21, 2016.

United States Congress (2008). *Congressional Budget Office Cost Estimate S.1695: Biologics Price Competition and Innovation Act of 2007, as Ordered Reported by the Senate Committee on Health, Education, Labor, and Pensions on June 27, 2007*. Congressional Budget Office. <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>, as of May 21, 2016.

White, Elisabeth (2014). *Spotlight on Biosimilars*. Presentation for the 11th Annual Future of the PBS Summit, 5 May 2014. Informa. <http://www.slideshare.net/informaoz/elisabeth-white-baker-mckenzie?utm_source=slideshow&utm_medium=ssemail&utm_campaign=download_notification>, as of May 21, 2016.

The Calculus of Convergence: Intellectual Property Rights for Pharmaceuticals and the Global Trade Agenda

by Christopher Sands

Introduction

The pharmaceutical industry is undergoing a period of profound change, buffeted by trends in demographics, technology, and the global economy that have upset a system of intellectual property rights, sophisticated regulatory scrutiny, and term-limited monopoly pricing that for decades has fostered the conditions for firms to innovate. This is the end of an era, not just in Canada, but worldwide.

Since 1986, pharmaceutical industry concerns have found a place on the agenda of trade liberalization negotiations. Today, following the collapse of the Doha Round of World Trade Organization-sponsored talks, bilateral, regional, and small multilateral trade negotiations all address the concerns of pharmaceutical firms in different ways. Still, it is not immediately obvious why trade negotiators are leading discussions of patent reforms rather than domestic legislators or members of the domestic patent bar.

This paper offers a short introduction to the international political economy of the pharmaceutical sector, and the forces driving change. It then considers the ongoing efforts to find a new global consensus that could permit pharmaceutical firms to innovate and operate profitably, as well as the potential consequences if they fail to arrive at a consensus. The options—even opportunities—that this state of affairs presents for Canada are included in a brief conclusion.

The role of intellectual property protection in pharmaceutical innovation

The pharmaceutical industry is being rapidly and radically restructured by a combination of new technologies, and demographic and economic trends, as populations in developed countries grow older due to longer lifespans and lower birth rates, with similar patterns beginning to appear in China, India, and other emerging markets, increasing demand for pharmaceutical innovation (Chandler, 2005). As a consequence, governments are also under pressure to simplify, expedite, and coordinate across national boundaries to lower the compliance burden on firms while maximizing the accessibility of pharmaceutical benefits to public health. Since the 1980s, trade negotiations have been a venue for addressing changes to the regulation of this sector, and today negotiators of the Canada–EU Comprehensive Economic and Trade Agreement (CETA), the Trans Pacific Partnership (TPP), and ongoing talks under the aegis of the World Trade Organization (WTO) in the aftermath of the Doha Round are grappling with pharmaceutical issues in new and creative ways.

A company that develops a new pharmaceutical drug has to secure intellectual property rights to the drug through the patent system as well as regulatory approval to sell the drug to the public. This dual-approval process is common to most markets, but reciprocal recognition is not common. This means that a company must initiate these two parallel approval processes in each of the markets in which it hopes to introduce the new drug with some degree of synchronization.

The 148 countries that are signatories to the Patent Cooperation Treaty (PCT) that was negotiated as the Paris Convention of 1978 allows any resident or national of another signatory country to file a single international application. This has the effect of a national patent application (and certain regional patent applications) in some or all PCT contracting states, including Canada, which became a signatory in 1990. The PCT is administered by the World Intellectual Property Organization, and while the PCT provides a benefit to originators in the form of expedited patent rights recognition, there is no corresponding coordination on regulatory approval.

Patent approval processes are similar in most countries that are members of the Organization for Economic Cooperation and Development (OECD)—a group of relatively developed and mature markets that are important consumer markets for pharmaceutical manufacturers. The authorities in these countries will confer a patent for a drug if it meets three criteria: originality (or novelty), meaning that the drug is truly something new; non-obvious (a US term; for the EU the standards it is called an "innovative step"), meaning that there is something inventive in the idea

or creation or process that is proposed to be patented; and utility, meaning that there is a specified use or purpose to the invention that could have a commercial value, making the certification of ownership significant to the person applying for the patent.

Patent examiners may require details of the process or formulation of a drug or specifics concerning the design and functioning of a medical device. This information is provided on a confidential basis by the applicant for a patent, but this information becomes public eventually, either when the patent right is granted or after a period specified by a national statute.

Individuals can apply for a patent for a new drug or device, or a new use for an existing drug or device, on the basis of initial evidence of potential utility, such as a study published in a medical journal or a report from a lab. This standard is lower than what is required to convince regulators that a drug is safe to be sold to the public, even when limited by prescription issued by a qualified medical professional. Regulators typically require evidence from clinical trials using humans (rather than animals or another substitute). The disparity is important and deliberate in order to encourage an innovator who thinks a drug might work to secure the rights to the innovation prior to undertaking the investment of time and resources to conduct trials.

Clinical trials can be expensive to conduct. The US regulator, the Food and Drug Administration (FDA), requires a three-stage clinical trial protocol for most pharmaceuticals. One recent estimate placed the cost of clinical trials through all three stages at US$1.3 billion per drug (Roy, 2012).

Another study found it cost an average of US$2.558 billion to win regulatory approval for a single drug (Tufts Center for the Study of Drug Development, 2014). The second, larger estimate reflects the time-cost of delays of up to ten years in the regulatory approval process. Both these figures are for approval in the US market only; regulators in other countries may accept the same clinical trial data used to win US approval, but in some cases will require additional testing before approving a drug for use in their respective markets.

Delays in regulatory approval for a drug that has been successfully patented mean that the pharmaceutical company that originated a drug cannot sell it and begin recouping its costs as quickly as it could with shorter delays. As a result, pharmaceutical originators have called on governments to provide "patent term restoration," an extension of intellectual property rights (IPR) for the full term (typically 20 years of exclusivity, although this varies by country) effective from the date of regulatory approval.

The asynchronous nature of patent rights and regulatory approval can affect originators in another way. A drug that has secured regulatory approval is the exclusive property of the patent holder for the duration

of the patent, giving the patent holder the exclusive right to produce and market that specific drug in that specific market. When the patent term expires, other firms can produce copies of the drug and market them where regulators have approved the drug for use. Although patent and regulatory approvals processes are parallel, regulatory approval does not expire (although it can be rescinded or altered if new medical evidence warrants, in which case the approval affects the originator and the copier of the drug alike).

Copies of patented medicines are called generic drugs in the case of chemical pharmaceuticals. A new class of drugs made from genetic material called biologics can also be copied, and the resulting medications are referred to as biosimilars. Biosimilar copies of biologic drugs are just beginning to enter the market and are being treated by US courts like generic drugs (Grant, 2015).

Although the costs of research and development of a new drug are high, as are the added costs of securing patent rights and regulatory approval, the period of patent exclusivity can allow a firm to recoup its initial investments by pricing the drug accordingly. However, there are obstacles confronting firms seeking to set prices at a level sufficient to recapture their initial investment.

The structure of the market for pharmaceuticals is one challenge. In many markets, there are a limited number of customers for a particular medication. First, there may be a limited number of potential patients for whom a drug is appropriate. Second, government health programs, large hospital and health care systems, and private insurers that must approve the purchase of a medication, are often able to exert downward pressure on drug prices (in effect, to act as an oligopsony (i.e., a market in which only a small number of buyers exist for a product). Third, in cases where governments are the exclusive health care provider, drug prices may be regulated with upper limits on unit prices that suppliers may charge.

Competition also limits the pricing power of a pharmaceutical originator once its period of patent-secured monopoly has ended. In the most direct case, once a generic or biosimilar alternative is available in the market, the opportunity to recoup the costs of drug development and approvals is constrained. Firms that produce copies of the original drug or medical device do not have to incur the research, development, patent or regulatory approval costs associated with the introduction of a new product, and so are able to price copies at a far lower level. Some insurers and government programs require medical professionals—and even patients—to choose a generic or biosimilar drug if it is available.

To forestall the entry of competitors into a market, pharmaceutical originators have in some cases sought a second patent for a drug on

the basis of a new use (utility) for which they have an existing patent. The practice of second patenting is known pejoratively as "evergreening" because it can allow an originator to have a second period of exclusivity for the new application, expanding the potential population of users and extending the period during which the originator can engage in monopoly pricing to recoup development costs.

Generic and biosimilar producers can challenge these patents in court, and they can also petition regulators to deny or delay the approval of a drug for a second use to limit the advantage of pharmaceutical originators. In doing so, generic and biosimilar firms have sought allies in government, civil society, medical professionals, private insurers, and the general public on the basis that monopoly pricing by originators effectively denies access to medication to patients with limited means. The moral resonance of this claim has been particularly profound in emerging markets, but in developed countries where governments bear the costs of public health care provision, the pecuniary interest in lowering pharmaceutical prices as quickly as possible has resounded powerfully as well.

Under the World Trade Organization Trade Related Intellectual Property (TRIPS) agreement, two articles are particularly important for the pharmaceutical sector: Article 27 and Article 31.

TRIPS Article 27 defines what may be patented, citing the standard criteria of originality, inventive step, and capacity for industrial application, but it provides for two important exceptions. Article 27 section 2 states:

> Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law. (World Trade Organization, 1986)

Protection of public order could lead to the denial of a patent for a drug to treat HIV–AIDS by a government (such as, for a time, South Africa's) bearing a prejudice against the infected. Exemptions on the basis of "morality" are not defined, and this exemption could be used to deny patents to abortifacient drugs, treatments for erectile dysfunction, or birth control drugs in some countries. Similarly, the protection of human, animal, or plant life, and the avoidance of "prejudice to the environment" are undefined and provide broad latitude to governments to deny a patent to particular pharmaceuticals. Article 27 section 3 erodes the protection for intellectual property for pharmaceutical firms even further, providing for an additional basis for exemptions:

> Members may also exclude from patentability:
>
> (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;
>
> (b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof. The provisions of this subparagraph shall be reviewed four years after the date of entry into force of the WTO Agreement. (World Trade Organization, 1986)

Hormonal therapies, biologics, and drugs based on modified genetic material (GMOs) could all be excluded from intellectual property protections under these broad provisions. For pharmaceutical originators, TRIPS Article 27 alone has the potential to vitiate the additional protections promised by TRIPS.

TRIPS Article 31 confirms the right of governments to issue "compulsory licenses" to generic manufacturers to produce copies of a patent medicine in the case of a public health emergency. The WTO has oversight over this clause, and a government can be challenged on its claim of an emergency by another WTO member government. Apart from emergency conditions, the TRIPs agreement binds signatory states to enforce private intellectual property rights with regard to pharmaceuticals (Boulet, 2000).

The role of governments as both the providers of patent rights and regulatory approval to enter the national market on one hand, and as purchasers (directly or indirectly) of pharmaceuticals on behalf of some or all citizens on the other hand creates an ironic dilemma from the perspective of originators. After all, a significant portion of the cost of a new pharmaceutical or device that must be recaptured by higher prices during the period of patent exclusivity is the cost of securing intellectual property rights (IPR) and regulatory approval. Governments both impose high costs on originators and then act in concert with copiers to undermine the originator's ability to earn the profit necessary to provide a return on the initial investments necessary to bring a drug to market. At the same time, governments must strike a balance between policies that encourage innovation through secure IPR and the need to constrain pharmaceutical costs to promote access to essential pharmaceuticals in the interest of public health (Brougher, 2014).

Since health care affects virtually all citizens directly or through their dependents, bureaucrats as well as politicians experience pressure to constrain the pharmaceutical originators' prices. Judicial systems are also not immune to such pressures, as cases brought by copiers or by patients to challenge patent terms, claims of benefits by the originator, or payment decisions by insurers (public and private) expose pharmaceutical originators to litigation. In Canada, courts have allowed generic manufacturers to challenge the utility basis for second patents and secure an immediate termination of the originator's IPR (Canadian Intellectual Property Council, 2011).

In the United States, generic drug manufacturers have used an administrative challenge procedure to attempt to invalidate or gain early termination of IPR for originators, leading originators to press for pharmaceutical patents to be exempted from administrative challenges altogether (Walker, 2015). Challenges would still be allowed in federal courts if the originators succeed in protecting their patents from the administrative challenge procedure, but US federal court reviews take longer and are more costly for challengers.

The irony in such cases from the originator's perspective is that after a court rules in favour of a plaintiff's challenge to a patent on the basis of utility, the plaintiff proceeds to produce and sell copies of the drug found lacking in utility. Yet the finding of insufficient utility is not a finding of zero utility; the insufficient utility may be determined by the court in relation to the originator's claims for the second application, and in any case does not relate to the utility asserted in the initial patent, which remains uncontested.

Another threat to the ability of pharmaceutical originators to recoup costs during their period of patent exclusivity comes from imported drugs. These may be copies (generic or biosimilar) or they may be the product of the originator, purchased for a lower unit price in one market and then exported to a higher-price market. This is possible because unit prices may vary by market due to the oligopsonistic structure of demand in that market, or due to prices set by regulators for a particular market. Prices may also differ across markets if the patent rights of the originator expire in one market before they expire in another. The result is downward pressure on prices in all markets through arbitrage (OECD, 2008). Since the intellectual property protected by a national patent is effectively returned to the market from outside the country during arbitrage, the phenomena has been called re-importation or parallel importation.

The US Congress debated legislation to make re-importation legal as a popular antidote to high prices for certain drugs as early as 2003 (Arfwedson, 2004). Citing lower prices for certain drugs on Canadian formularies, the Congress sought to permit US citizens to freely import certain

drugs from Canada, often through online pharmacies. This would not directly alter the patent right of the pharmaceutical originator to profit from a particular drug, but would reduce the value of the patent in a country like the United States where firms could count on charging higher prices to recoup costs even when facing price limits in other markets.

Firms that originate pharmaceuticals must also seek data protection commitments from the regulators who govern market access. Pharmaceutical companies must submit details of a drug's composition as well as the results of their own clinical trials. Regulators receive access to some quantity of the drug for independent testing and additional trials. The data involved is typically restricted for a period of time, but eventually becomes available to other researchers. At this point, two new risks for pharmaceutical originators emerge (Pugatch, 2004). This data can in many cases be used to duplicate the drug for sale as a generic or biosimilar product, so if there is any market in which the originator has not secured its IPR, copies can be made and sold, and there is some risk of counterfeit drugs being exported into markets where the firm has patent exclusivity, undermining the ability of the originator to recoup costs via pricing. Additionally, the data, particularly concerning the clinical trials on human subjects, becomes accessible for litigation.

Litigation is a particularly significant source of risk in the United States, where companies can be subject to punitive fines awarded by juries whose sympathies rest with a sick patient or with families of the deceased who blame a drug and its originator for injury or loss (Garber, 1993). Class action suits can allow one case of injury to metastasize into a hypothetical class of possible victims that a jury might consider when rendering a figure for damages. Since the pharmaceutical originator is the only firm to have sought and received regulatory approval for a drug, it faces such litigation risk alone; generic and biosimilar manufacturers can only be targeted if they deviate from the regulatory-approved formula.

Erosion of the term of patent exclusivity for the pharmaceutical originator by bureaucratic, legislative, or judicial action has put these firms on the defensive. At the same time, three broad trends are transforming the pharmaceutical industry worldwide.

Demographics

Populations in developed countries are aging due to lower birth rates and longer lifespans, and older individuals are more likely consumers of pharmaceuticals (US National Institute on Aging, 2012). The elderly in developed societies have greater access to pharmaceutical options due to their own resources and because of wealth transfers from younger genera-

tions, often mandated by governments. This has expanded the potential market for expensive pharmaceutical options, which address medical conditions and help manage chronic conditions while giving patients a better quality of life. The larger the proportion of the population that is elderly and in need of expensive pharmaceuticals, the greater the financial burden on younger workers, who in turn tend to blame government (for the taxes that fund the wealth transfers) instead of their elders. Lowering health care costs has accordingly become a priority for the democratic governments of the developed world.

While this demographic trend is familiar to Japanese, Europeans, and North Americans, many emerging markets are showing signs of aging as well and for similar reasons (e.g., lower birth rates and longer lifespans). Yet for many of these societies, such as China, India, and Brazil, there is less financial capacity for intergenerational wealth transfers, and lower absolute levels of saving and other assets accessible to the elderly. In these countries, governments have sought "access to medicines" on behalf of their citizens through discounts from pharmaceutical originators, aid programs to finance medications in response to health crises and epidemics (such as to combat malaria or HIV–AIDS), and adjustments to IPR or regulatory systems to favour consumers and low-cost manufacturers (of generic or biosimilar copies of patented medications and devices) (t'Hoen, 2002).

Innovation

The nature of innovation and its dissemination has changed dramatically in recent years. Advanced manufacturing and automation has made it possible to quickly and cheaply design (or reverse engineer), mass produce, and distribute new products to markets worldwide very quickly (Shipp, 2012). This places new pressures on IPR from counterfeiters, imitators, and other competitors who can exploit any gap in IP rights or regulatory approval to capture market share that would once have been safely within the preserve of the patent holder (Kiriyama, 2011).

Peter Thiel and others have complained that this has led firms to seek innovations on the margins of existing products for which they have secure IPR, such as process changes and new applications, instead of "breakthrough" innovations that create new markets and new demand (Thiel, 2014). This is certainly a characteristic of some firms in the pharmaceutical and medical device sector, where the high costs of research, development, patent, and regulatory approval are both rising and becoming more difficult to recover through pricing during the limited period of patent exclusivity that is also being eroded by numerous trends. Marginal improvements or tweaks to existing drugs, or new applications for drugs

under secure IPR and existing regulatory sanction offer a better risk-adjusted return on investment than does the expense and effort involved in developing an uncertain new drug.

Globalization

The pressures on the pharmaceutical originating industry are leading to a globalization of the sector that favours large firms with the capacity to spread risk across a larger portfolio of drugs that have secure IPR and regulatory approval in as many markets as possible simultaneously. Boutique firms with smaller portfolios and presence in a limited number of markets are more vulnerable to patent, regulatory, counterfeiting, and re-importation risks, which make it difficult to finance new drug development. Often, when such firms do innovate, they seek to sell a new drug to a global firm that can better realize its market value potential due to its advantages of size and scope.

Globalization of the pharmaceutical sector is also being driven by consumers and the fluid sharing of information about new pharmaceutical options that occurs across national borders. Whereas news of the latest medical breakthrough used to disseminate through scholarly publications and a handful of well-traveled experts and those with the means to travel for treatment, now that news is readily available on the internet. Patients in rural and remote areas expect pharmaceutical options as quickly as those in world capitals.

As global firms consolidate, they are pressuring governments to standardize and synchronize patent systems, building on the PCT to "single-window" applications (i.e., to conduct simultaneous reviews by multiple patent authorities, get patent agencies to reciprocally recognize IPR, and standardize patent terms and protections). In addition, global firms are seeking to shrink regulatory approval times by promoting greater mutual recognition of approvals by the regulators in different countries.

All three previously cited trends (demographics, innovation patterns, and globalization of the originating pharmaceutical industry), have combined to place pharmaceutical concerns about IPR and market access (via regulatory approval) on the international trade agenda.

Toward a global standard for IPR: The WTO, TRIPS, and the TPP

During the Uruguay Round of what was then known as the General Agreement on Tariffs and Trade (GATT) from 1986 to 1994, the three trends

reshaping the pharmaceutical industry led governments to consider pharmaceutical sector trade for the first time. The final Uruguay Round agreement eliminated tariffs on imported pharmaceuticals, which subsequently led to an increase in parallel imports (re-importation) as well as generic drugs, both of which entered markets where originators held IP rights that remained in force.

The Agreement on Trade Related Intellectual Property Rights (TRIPS) was negotiated alongside the Uruguay Round and became part of the World Trade Organization (WTO) agreements (Boulet, 2000). This meant that it was binding on all WTO member states and disputes related to IPR could be adjudicated by governments within the WTO dispute settlement mechanisms.

The TRIPS Agreement standardized the patent term of exclusivity for an originator to 20 years, and called on governments to respect and enforce private IPR. Article 31 of the TRIPS Agreement confirmed the right of governments to issue compulsory licenses for domestic manufacture of generic copies of medicines still under patent in the case of a declared public health emergency, but created a mechanism for review of emergency declarations by the WTO at the request of another member state government. This compromise addressed concerns over access to "essential" medicines in times of crisis, but attempted to provide some discipline through international oversight that would prevent the abuse of the exemption.

The TRIPS compromise was criticized by many public health officials in developing countries and development activists who cited the rapid spread of HIV–AIDS in Africa, noting that the most effective treatments for those diagnosed as HIV positive were new pharmaceuticals under patent, and many of the most affected countries lacked the domestic capacity to produce generic copies of such medicines in any case; in effect, they had no firm to issue a compulsory license to. WTO members at the Seattle meeting, and later as part of the Doha Round negotiations, agreed to discuss amending the exemption to allow for the importation of generic copies under compulsory licenses (t'Hoen, 2002).

The Doha Round negotiations, launched in 2001, progressed slowly and ultimately failed to reach an agreement. As a result, several governments pursued negotiations on trade liberalization bilaterally and regionally or multilaterally at the same time as the Doha Round, opening up a new option for addressing pharmaceuticals.

In 2005, the United States, Canada, and Mexico launched a negotiation on the regulatory and security barriers to market access. The negotiation attempted to revisit some of the issues not successfully dealt with in the North American Free Trade Agreement (NAFTA). The Security

and Prosperity Partnership of North America (SPP) established 20 government-to-government working groups. In 2006, private sector groups created the North American Competitiveness Council to press the three governments on issues of concern to business (Anderson, 2007). The governments considered ways to lower the cost of pharmaceutical drug approvals by regulators by agreeing to a common application, parallel regulatory consideration, and even mutual recognition of some drug approvals as well as sharing clinical trial data. Limited progress was made on these ideas before the SPP was terminated by the Obama administration in 2009.

The Obama administration saw merit in continued talks with Canada and Mexico on security and regulatory cooperation, and chose to continue these talks on a dual-bilateral basis, with regulatory cooperation talks taking up pharmaceutical issues between the United States and Canada in 2011 (Sands, 2011). The agenda was again to lower the cost of duplicative regulatory measures for pharmaceutical originators, rather than harmonizing pharmaceutical IPR systems in the two countries.

IP concerns were, however, a source of friction between the United States and Canada for products ranging from software to pharmaceuticals. The United States Trade Representative placed Canada on its "priority watch list" for intellectual property piracy beginning in 2009 and the US government pressed Canada for changes to its intellectual property protection statutes (Office of the United States Trade Representative, 2010). In 2014, the Parliament of Canada approved the *Copyright Modernization Act* and in the process addressed some US concerns, but not in the area of patent medicines (Gardiner Roberts LLP, 2014).

Tensions between international pharmaceutical originators and the government of Canada subsequently worsened due to judicial action. Canadian courts granted patent termination to domestic generic manufacturers in a handful of cases on the basis of instances in which claims made by pharmaceutical originators to secure a second patent term on the basis of a new use for the patented drug were denied. The Canadian courts found in favour of plaintiffs that the patent holder had not fulfilled its "promise" of utility.

As a result of one such ruling, Eli Lilly and Company filed an investor–state dispute claim against the government of Canada under Chapter 11 of the NAFTA, alleging that the invalidation of its Strattera and Zyprex pharmaceutical patents by Canada was inconsistent with Canada's commitments under NAFTA (Canada, Foreign Affairs, Trade and Development, 2015). This case is still pending as of this writing.

Canada came under pressure to address pharmaceutical IP protection during negotiations with the European Union that led to the announcement of the Canada-EU Comprehensive Economic and Trade

Agreement (CETA) in 2014. Although the CETA remains unratified, its text commits Canada and the EU to enforce private IP for pharmaceuticals consistent with TRIPS (with 20 year exclusivity), and provides for patent restoration and common standards for data exclusivity (Dawson, 2015).

The United States joined ongoing negotiations with Australia, Brunei Darussalam, Chile, Malaysia, New Zealand, Peru, Singapore, and Vietnam on a Trans Pacific Partnership (TPP) in 2008 during the Bush administration. In 2010, the United States sought to have Canada, Mexico, and Japan join the TPP, and each of the three was subsequently welcomed to the negotiating table by the other governments.

Pharmaceutical issues have been a contentious issue in TPP talks. The draft text released by the United States Trade Representative confirms that the United States had largely succeeded in getting other TPP countries to accept the TRIPS language for protection for pharmaceutical IP (Office of the United States Trade Representative, 2015). Concerns over possible restrictions on the use of compulsory licenses for the importation of generics have been raised by advocates for access to "essential medicines" throughout the talks, and re-emerged on the basis of another leaked draft in July 2015 (Grunwald, 2015). These did not remain in the final text, however (Office of the United States Trade Representative, 2015). The process of ratification by the 12 TPP governments could yet lead to more changes to this text, particularly if the US Congress delays action on the TPP until after a new US administration takes office in January 2017; a similar delay in ratification of NAFTA allowed the Clinton administration to add side agreements to NAFTA as it had been negotiated by the George H.W. Bush administration.

At the same time, United States negotiations with the European Union seeking to establish a Transatlantic Trade and Investment Partnership (TTIP) are expected to address pharmaceutical IP standards. Although both the United States and the European Union are home to major pharmaceutical originator firms as well as generic and biosimilar manufacturers, they cannot by themselves be certain to set a global norm for pharmaceutical IPR with TTIP alone.

This prevalence of pharmaceutical issues in trade talks reflects the compelling nature of the trends reshaping the industry. Globalization is taking place as generic versions of patent medicines move between national markets in increasing volumes. The extant system under which originators could recoup research, development, patent, and regulatory approval costs in developed country markets through monopoly pricing is under pressure from governments seeking to lower costs associated with health care. Innovation is occurring at a rapid pace, but also allowing copies of patent medicines with increasing ease while attempts to extract additional

revenue from existing drugs by extending patents on the basis of new uses for a medicine are being challenged by novel legal arguments in Canada and other markets.

Behind all of these concerns, the demographic shifts in both developed and developing countries, prompted by lower birth rates and longer lifespans, are expected to increase demand for pharmaceutical breakthroughs—and price reductions.

Positions of selected governments

The positions of the governments in the various trade negotiations of recent years permit a simplified typology into three main groups.

The first group consists of *accommodators*, and includes the United States, joined on some issues by the European Union and Japan. It is the group most favourable to the concerns of the major international pharmaceutical originators. Although these governments are also seeking to lower pharmaceutical prices and health care costs in their respective home markets, they also impose considerable costs on pharmaceutical originators through the compliance burden associated with securing patent rights and regulatory approval. In the United States in particular, litigation has challenged IP associated with pharmaceuticals that have won both patent and regulatory approvals, creating additional costs and risk for originators. Pharmaceutical firms seek relief on these costs from governments, while governments seek relief on prices—a natural bargain, perhaps, and one that the United States is pursuing through regulatory cooperation with Canada.

Yet as globalization drives firms toward one price in all markets in response to arbitrage pressures from re-importation and generic and biosimilar competition, the United States and other accommodators seek to secure internationally consistent IPR protections to increase the value and lower the uncertainty for pharmaceutical originators concerned about recouping costs. This is not a solution to the larger cost issues, but it does provide some relief at the margins for firms without reducing the thoroughness of regulatory reviews or eliminating the downward price pressures of globalization, which will benefit these governments and their citizens as well. For accommodators, the goal is to strike a balance that sustains the necessary conditions for pharmaceutical innovation while shifting the market for pharmaceutical drugs toward greater competition and access (via lower prices).

The second group consists of *bargainers:* developed countries with some generic or biosimilar production capacity, but few (if any) origin-

ators. Under pressure from pharmaceutical originators and accommodator governments to change domestic IP and regulatory systems to conform to new international standards and norms—often based on the United States's own approach—the bargainers see harmonization of international rules for pharmaceuticals as likely, and perhaps even desirable. However, they seek to trade their efforts to bring their policies into alignment with any new international norm for concessions in other areas. Domestically, this is necessary to show the benefit to their constituents of moving from the familiar national approach to something new that will clearly benefit the international pharmaceutical originating firms which are foreign, or have a limited presence in the domestic market.

The context of trade negotiations has traditionally fostered bargaining, and the shift of pharmaceutical IP concerns onto the trade liberalization agenda made the emergence of bargainers logical. Their demands are also manageable by accommodator governments willing to give concessions in other areas in order to secure a strong international IP regime for pharmaceuticals.

The third group of governments is the *mendicants*, seeking access to patent medicines at low or concessionary prices. For many, compulsory licensing has been of limited value due to the lack of domestic capacity to copy drugs and produce them in quantities sufficient to supply local needs. To some extent, the needs of mendicant countries can be met by developed country aid programs such as the US President's Emergency Plan for AIDS Relief (PEPFAR) set up during the George W. Bush administration, or by concessions negotiated with pharmaceutical firms themselves.

Yet in the trade negotiation process, the large number of mendicant governments poses a threat to a fragile consensus that would foster the emergence of an international pharmaceutical IP regime of norms and standards sought by accommodators and acceptable (at some price) to bargainers.

While the momentum toward an international IP consensus for pharmaceuticals is strong, groups working against it include generic and biosimilar firms who would lose out, as well as development and public health advocates whose commitment to saving lives outweighs a commitment to further innovation and even, in some cases, market capitalism. Combined with the moral force of the mendicant case based on need, the momentum could shift against a global pharmaceutical IP regime emerging from any of the current trade negotiations.

This failure would not alter the trends described above: the pharmaceutical industry would still fall under pressure for global price convergence as copying even complex patent medicines increases and arbitrage across markets grows. Without a means to recover capital investments in

research, development, and patent and regulatory approval, investors will shift capital away from the pharmaceutical sector. The resulting loss of future cures is incalculable.

Private sector positions and options

The two scenarios—of securing or failing to secure pharmaceutical IPR within the international trade system—are presented starkly above in order to highlight the stakes. It should be clear to firms in the industry that the legacy model whereby pharmaceutical originators were permitted a regulated monopoly in order to recoup investments in research, development, and patent and regulatory approval—similar to the model used to encourage private investors to develop telephone and cable networks—is under threat. The status quo will not hold.

For this reason, among others, there has been industry consolidation in recent years, with the result that the pharmaceutical originating sector is now dominated by a small number of large firms whose size gives them an ability to spread risk and survive.

It should be recognized that accommodator governments, including the United States, are accommodating change, not preserving the existing order. Yet this approach is the friendliest to the survival and thriving of the pharmaceutical originators. With skill and tenacity, the accommodators can also win over the bargainers, or at least the most important of these.

The strong moral case of the mendicant governments, however, has resonance with citizens of both the accommodator and the bargainer countries. For a global IP consensus to be sustained, some compromise with the mendicant governments, or a sufficient number of them, will be necessary.

This points to the weakness of seeking a durable set of norms in bilateral and regional multilateral trade negotiations. While a US–EU agreement on pharmaceutical IP sealed in a future TTIP would be a significant achievement, it would remain open to the mendicant challenge. This is why the logic of TRIPS, abandoned when the Doha Round collapsed for other reasons, was revived in the TPP and still holds.

While ratification of the TPP will take time, particularly given the ongoing US elections, the pharmaceutical originating firms should not rely for a solution on possible changes to the TPP, or any other current negotiation. This analysis of the forces driving change in this sector globally points to another promising option that might be pursued simultaneously: government reforms of existing patent and regulatory approval systems that cut costs and expedite decisions.

The accommodator governments are offering a kind of relief that is in part a way to avoid making major changes to their own processes in these areas. Today, the international pharmaceutical originator firms are villains to the public, which objects to the high prices of original medications. Yet those high prices are the result—at least partially—of the government's processes. Improvements to those processes of the type being discussed by Canada and the United States in their Regulatory Cooperation Council would permit lower prices at home and abroad. And although difficult, these reforms could address the needs of mendicant countries as well. Bargainer governments like Canada's are being asked to undertake difficult domestic policy reforms to establish international IPR norms for pharmaceuticals; why not press accommodator governments to do likewise?

Implications for Canada

There is an active debate in Canada over the future of the domestic IPR system and the role of pharmaceuticals in national health and economic development. The brief overview in this chapter, which focuses more on global trends than the Canadian domestic market, provides the basis for two brief observations about the implications for Canadian policymaking in this area.

First, *change is inevitable*. Canada may bargain, but it will sooner or later need to conform to an international IPR consensus on pharmaceuticals if and when one emerges. Therefore, its bargaining should be aimed at arriving at a deal with the accommodators, led by the United States, which is defensible as the best deal possible for Canadians.

Second, *reform of domestic government processes is important*, not just to pursue the NAFTA goal of a single market for goods and services in North America, but also to address the concerns of developing countries. Shortening the length of time it takes for patent and regulatory approvals, providing for simultaneous and coterminous approvals across multiple markets through governmental regulatory cooperation, and employing big data analytics to track biologic performance and sharing data on such personalized medicines among regulators could all reduce the costs firms need to recover, and provide a basis for lower prices. The US-Canadian Regulatory Cooperation Council is an under-resourced, under-appreciated forum that could provide innovative reforms of regulatory approval processes that cut costs and improve public sector productivity—with profound implications for growth as well as health.

The situation in which Canada now finds itself is at the center of a global effort to find the calculus of convergence that will produce a consensus for new global norms and a stable pharmaceutical sector capable of generating innovation for decades to come. In that calculation, Canada is not the victim of change, but a potential contributor to reform.

References

Anderson, Greg, and Christopher Sands (2007). *Negotiating North America: The Security and Prosperity Partnership*. Hudson Institute.

Arfwedson, Jacob (2004). *Reimportation (Parallel Trade) in Pharmaceuticals*. Policy Report 182. Institute for Policy Innovation.

Boulet, P., J. Perriens, F. Renaud-Théry, and G. Velasquez (2000). *Pharmaceuticals and the WTO TRIPS Agreement: Questions and Answers.* UNAIDS and World Health Organization.

Brougher, Johanna T. (2014). *Intellectual Property and Health Technologies: Balancing Innovvation and the Public's Health*. Springer.

Canada, Foreign Affairs, Trade and Development (2015). *Cases Filed Against the Government of Canada: Eli Lilly and Company v. Government of Canada. NAFTA – Chapter 11 – Investment*. <http://www.international.gc.ca/trade-agreements-accords-commerciaux/topics-domaines/disp-diff/eli.aspx?lang=eng>, as of September 16, 2015.

Canadian Intellectual Property Council (2011). *Innovation for a Better Tomorrow: Closing Canada's Intellectual Property Gap in the Pharmaceutical Sector.* Canadian Chamber of Commerce.

Danzon, Patricia M., and Andrew J. Epstein (2012). Effects of Regulation on Drug Launch and Pricing in Interdependent Markets. In Kristian Bolin and Robert Kaestner (eds.). *The Economics of Medical Technology* (Emerald Group Publishing Ltd): 35–71.

Dawson, Laura (2015). *Slow and Steady Will Not Win the Race: Trade Negotiation, IP Protections and Canada's Pharmaceutical Industry*. Dawson Strategic.

Fernandez, Dennis S., James Huie, and Justin Hsu (2007). The Interface of Patents with the Regulatory Drug Approval Process and How Resulting

Interplay Can Affect Market Entry. In A. Krattiger, et al. (eds.) *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices*. Vols. 1 and 2. (University of California Davis): 965–971.

Garber, Steven (1993). *Product Liability and the Economics of Pharmaceuticals and Medical Devices.* RAND Corporation.

Gardiner Roberts LLP (2014). *Canada's Copyright Modernization Act: Notice and Notice Regime to Take Effect January 2015.* Gardiner Roberts LLP.

Grant, Charley (2015, September 4). Big Pharma's Biosimilar Headache. *Wall Street Journal:* C8.

Grunwald, Michael (2015, July 1). Leaked: What is in Obama's Trade Deal – Is the White House Going to Bat for Big Pharma Worldwide? *Politico*.

Iacobucci, Edward M. (2011). *Innovation for a Better Tomorrow: A Critique*. Canadian Generic Pharmaceutical Association.

Kiriyama, Noboru (2011). *Trade and Innovation: Pharmaceuticals*. OECD Trade Policy Working Papers, No. 113. OECD. <http://dx.doi.org/10.1787/5kgdscrcv7jg-en>, as of July 13, 2016.

Lippoldt, Douglas (2006). *Intellectual Property Rights, Pharmaceuticals and Foreign Direct Investment*. Policy Brief. Paris: Groupe d'Economie Mondiale de Sciences Po.

Office of the United States Trade Representative (2010). *2009 Special 301 Report*. US Government Printing Office.

Office of the United States Trade Representative (2015). Trans-Pacific Partnership Full Text. United States Trade Representative. <https://ustr.gov/trade-agreements/free-trade-agreements/trans-pacific-partnership/tpp-full-text>, as of July 13, 2016.

Organisation for Economic Cooperation and Development (2002). *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies.* OECD.

Organisation for Economic Cooperation and Development (2006). *Innovation in Pharmaceutical Biotechnology: Comparing National Innovation Systems at the Sectoral Level*. OECD.

Organisation for Economic Cooperation and Development (2008). *Pharmaceutical Pricing Policies in a Global Market*. OECD.

Pugatch, Meir Perez (2004). Intellectual Property and Pharmaceutical Data Exclusivity in the Context of Innovation and Market Access. *ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines*. Bellagio.

Roy, Avik S.A. (2012). *Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials.* Project FDA Report no. 5 (March). Manhattan Institute.

Sands, Christopher (2011). *The Canada Gambit: Will it Revive North America?* Hudson Institute.

Shipp, Stephanie S. (2012). *Emerging Global Trends in Advanced Manufacturing*. Institute for Defense Analyses.

Silverman, Ed (2014, October 16). Trade Talk Documents Suggest Access to Medicines May Become Harder. *Wall Street Journal*.

Thiel, Peter, and Blake Masters (2014). *Zero to One: Notes on Startups, or How to Build the Future*. Crown Business.

t'Hoen, Ellen (2002). TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond. *Chicago Journal of International Law:* 27–46.

Tufts Center for the Study of Drug Development [CSDD] (2014, November 18). Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion. News release. CSDD.

US National Institute on Aging (2012). *Global Health and Aging*. World Health Organization and US Department of Health and Human Services.

Walker, Joseph (2015, September 1). Patent Rule Would Raise Drug Costs: Congressional Estimate of Proposed Change to Law Adds to Battle over Way to Challenge Rights. *Wall Street Journal*: B1.

Weisman, Jonathan (2015, July 30). Drug Patents Are a Hurdle for U.S. in Trade Talks. *New York Times*: B1.

World Trade Organization (1986). *Annex 1C: Agreement on Trade-Related Aspects of Intellectual Property Rights.* World Trade Organization. <https://www.wto.org/english/docs_e/legal_e/27-trips.pdf>, as of July 13, 2016.

Unique Aspects of Patents for Medical Innovation: Recent Research Developments

by Tomas J. Philipson[1]

Introduction

It is often argued that intellectual property (IP) spurs innovation by raising the rewards for discovery, but it does so by granting a monopoly in the event of discovery. According to classical theory (Nordhaus, 1969), the benefits of additional research and development (R&D) induced by a patent must be weighed against the costs of the loss of output from a patent monopoly. This classical view of the effects of patents implies that the deadweight loss of monopoly is what limits the value of patents and therefore predicts that patent expirations will always lead to increased competition, lower prices, and higher output.

Although some of these classic effects of patents are present for medical innovation, recent research suggests that innovation into medical products leads to some unique and peculiar aspects that are not present in other industries. This paper reviews aspects of these recent developments and argues that they are central to evaluating the effects and desirability of domestic intellectual property policies. The discussion here is highly selective although we attempt to refer the reader to more exhaustive reviews for further readings. For example, Malani and Philipson (2012) provide a

[1] I am thankful to Steven Globerman and workshop participants at a Fraser Institute symposium on intellectual property in the health care sector, held on September 18, 2015, for comments that improved the paper.

review of the regulatory aspects of medical product markets and Goldman and Lakdawalla (2011) provide an excellent review of the large literature on IP and medical innovation. Rather, the purpose here is to highlight some specific recent research developments that bear on the consequences of IP policies for innovation in medical product markets.

Domestic issues in patents and innovation

The standard analysis of patent protection argues that ex-post static efficiency should be sacrificed for ex-ante dynamic efficiency. Ex-post, output is inefficiently restricted by the marked-up prices the patent-monopolist charges, but this is efficient dynamically because investments are made in R&D to obtain the profits induced by subsequent monopoly power. Patents are not ideal compared to the utopian state where rewards of the total societal value of an innovation could be awarded without monopoly distortions, but such rewards are impossible to implement in practice. Various factors that raise profits ex-post, such as pricing or quantity through market size, will raise the amount of R&D undertaken to obtain those profits. The empirical analysis of the direction of these standard effects confirms this classic analysis of the effects of patents (Goldman and Lakdawalla, 2011). In this chapter, we discuss two unique aspects of the effects of intellectual property for medical innovations that have been analyzed recently in the academic community.

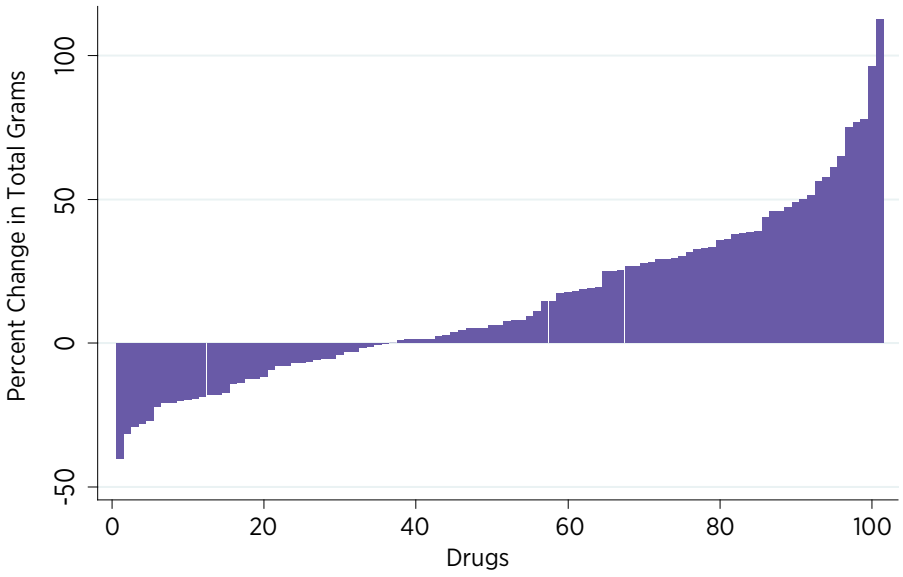
Marketing and patents

According to standard analysis of R&D benefits, a patent system must be weighed against the associated output lost to patent monopolies, which reduce price competition. This analysis implies that patent expirations always lead to increased competition, lower prices, and higher market output.

In light of this, Lakdawalla and Philipson (2012) present the surprising evidence shown in figure 1. The figure depicts the percentage change in quantity—comparing 6 months before patent expiration to 6 months after—for a sample of US pharmaceutical products whose patents expired between 1992 and 2002. For about 40% of drugs, output actually falls after patent expiration, and expands only modestly for many others.

The figure suggests there may be more to a patent expiration than the end of monopoly pricing alone, and consequently more to the welfare effects of IP protection. Lakdawalla and Philipson argue that the standard analysis of IP must incorporate various aspects of non-price competi-

Figure 1: Distribution of Quantity Changes by Molecule, from Patent Expiration to One Month after Expiration



Source: Lakdawalla and Philipson, 2012.

tion, which may reinforce or mitigate the effects of monopoly pricing. For example, while monopolists have incentives to restrict quantity through higher prices, they may also have different incentives to promote their product through advertising and to vertically integrate with upstream or downstream firms. These forms of non-price competition can change the efficiency impact of IP regulations.

Motivated by this idea, the analysis examines the effect of marketing—a particularly important form of non-price competition—on the static and dynamic efficiency of patents.[2] Patent expirations decrease the private returns to marketing, which disappear when goods are sold at marginal cost. As a result, expirations may actually reduce output, if they decrease marketing effort by enough to offset the impact of price reductions.

[2] Different forms of non-price competition merit separate analyses. For example, monopoly has a range of possible effects on quality provision. Mussa and Rosen showed that monopolists will "over-differentiate" their product and induce a lower quality choice by consumers (Mussa and Rosen, 1978). Subsequent authors have demonstrated how these results can be altered or even reversed under different specifications for demand (Gabszewicz and Wauthy, 2002).

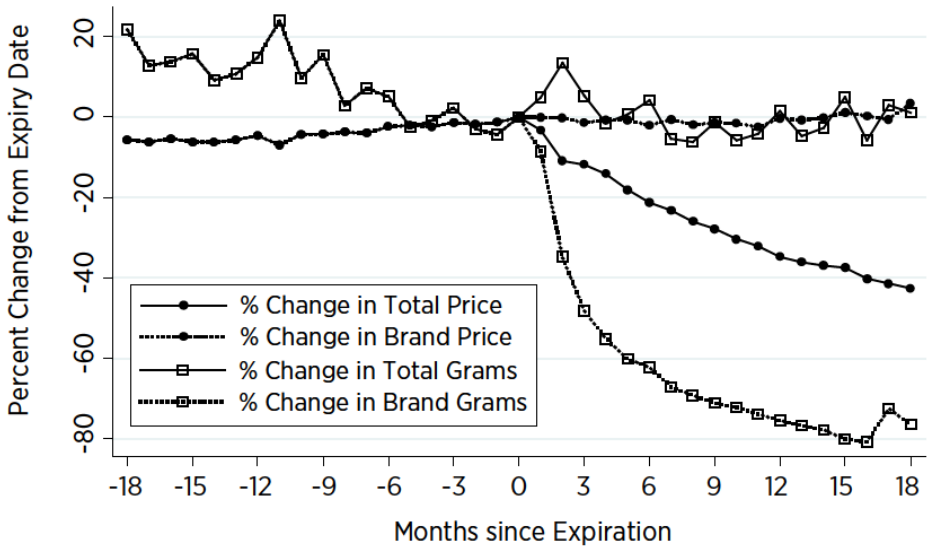
To assess the quantitative importance of these arguments more fully, Lakdawalla and Philipson estimated the impact of marketing on welfare using patent expirations in the US pharmaceuticals market, between 1990 and 2003. This industry is a natural choice for empirical analysis of R&D and marketing because it is among the highest-spending industries in both categories. The industry spends approximately 15% of sales on marketing, and 16% of sales on R&D.[3] By comparison, about 2% and 3% of US GDP are allocated to advertising and R&D, respectively, for the average industry.

Figures 2 and 3 differentiate the effects by amount of advertising. The figures are based on data from 101 molecules with patents that expired between 1999 and 2002. The source of the data is the IMS Generic Spectra database. The graphs show the percent change between the month of patent expiration and the month shown on the x-axis. In all cases, price is per gram. A fully advertised drug has at least one month of nonzero samples dispensed, at least one month of nonzero detailing visits, and at least one month of nonzero medical journal advertisements. Each figure depicts monthly time series, relative to the month of patent expiration, for branded quantity, branded price, total quantity, and total price, at the molecule level. Figure 2 depicts these trends for molecules that are advertised, while figure 3 does so for molecules that are not. For all drugs, price declines steadily after the month of expiration. For the non-advertised drugs, quantity rises fairly steadily over this period as well. However, for the advertised drugs, quantity appears flat after patent expiration. This suggests patent expirations may decrease demand among the advertised drugs, but not among their non-advertised peers.

Lakdawalla and Philipson estimated these effects more formally using the timing of patent expirations as instruments for the supply price and marketing incentives of a molecule. Changes in supply induced by patent expiration allow us to identify the demand for drugs as a function of both price and advertising effort. The estimated demand function implies that in the short-run (the first five months after expiration), output falls after patent expiration because the reduction in advertising more than offsets the reduction in price. This output loss is estimated to cost consumers roughly $1 million per month for each drug whose patent expires. Not until several years have elapsed does the price effect dominate the reduction in advertising. In the long-run, patent expiration benefits consumers, but the reduction in advertising reduces the total gain to consumers from patent expiration by about 30%. In the long-run, patent expiration increas-

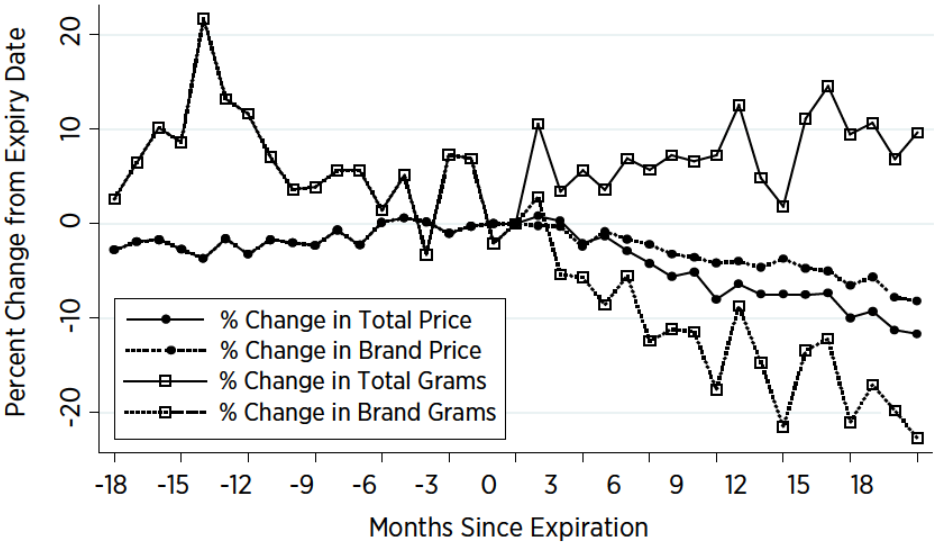
[3] Many drugs have seen dramatic increases in direct-to-consumer advertising (DTC) since the 1997 change in FDA guidelines on such advertising. The guidelines recommend providing patients with easy access to a product's approved labeling via a telephone number, website, printed material, and health care professional.

Figure 2: Mean Trends in Price and Quantity for Fully Advertised Drugs



Source: Lakdawalla and Philipson, 2012.

Figure 3: Mean Trends in Price and Quantity for Drugs Not Fully Advertised



Source: Lakdawalla and Philipson, 2012.

es quantity, thereby benefiting consumers. However, even from a long-run perspective, monopoly marketing provides benefits to consumers. We estimate that the value to consumers is roughly 20% to 25% of total monopoly revenue, roughly on par with the firms' costs of marketing. Therefore, even if firms did not benefit from marketing, the latter would be approximately welfare-neutral.

Cost effectiveness analysis and patents

Given the large and growing share of resources devoted to health care, many governments are grappling with how to best assess and adopt new medical products contributing to the observed growth in spending (Newhouse, 1992). In many countries, the major approach put forth to date has been the use of cost effectiveness (CE) criteria to guide the adoption of new and existing technologies. As the name suggests, CE analysis offers policy-makers an important means to allocate often scarce health care resources based on the costs and benefits of available medical technologies.

The extensive role of such criteria is particularly stark in many Westernized countries outside the US, e.g., the UK's National Institute for Clinical Excellence (NICE) and Australia's Pharmaceutical Benefits Advisory Committee (PBAC), both of which have been reported to follow implicit CE thresholds in technology adoption decisions. Such thresholds dictate that technologies will be adopted when their benefits, often measured by the quality-adjusted years of life they provide, outweigh a given level of costs. In Australia, for example, only 2 out of 26 submissions were accepted for reimbursement where their cost per life-year-saved exceeded $57,000; similarly, only 1 out of 26 submissions was rejected where the cost per life-year-saved was less than $32,000 (Bethan, Harris, and Mitchell, 2001). Although the US Centers for Medicaid and Medicare (CMS) do not use explicit considerations of cost effectiveness, it is reasonable to infer that technologies that cost more and have less of a health impact receive greater scrutiny before they are adopted.

Previous literature has established the positive role that CE analysis can play in allocating health care resources efficiently (Drummond, O'Brien, Stoddart, and Torrance, 1997; Garber and Phelps, 1997; Gold, Siegel, Russell, and Weinstein, 1996). While this literature demonstrates a solid economic foundation for using CE analysis to guide medical decision-making after a technology has been developed, less attention has been given to the incentives these criteria induce for bringing technologies to market in the first place. Put differently, spending on highly cost-effective technologies, i.e., those for which the static benefits far outweigh the costs, is routinely considered to be an appropriate use of health care funds.

If the observed cost-effectiveness of these technologies were lowered, e.g., through higher prices paid to innovators, would current and future patients be worse off? The answer to this question depends on the trade-off central to expensive, emerging technologies: the increased welfare of current patients due to adoption of only cost-effective technologies versus the decreased welfare of future patients due to the disincentives for innovation that such price control policies induce.

Contrary to previous literature, we assess CE analysis in a dynamic context—one that considers both its appealing properties after a technology has been developed as well as its effect on the R&D incentives crucial to technological change. In several respects, the CE thresholds in place in many countries resemble other mechanisms designed to regulate prices in other industries, such as rate-of-return regulations or straight price controls. In this sense, our recommendations are closely related to ongoing policy discussions of the role such cost-containment procedures may play in limiting incentives to innovate. While these procedures may increase social welfare through reduced prices once technologies are developed, their potentially negative effects on innovation are equally well understood (see, for example, US Dept. of Commerce, 2004). This is, in fact, the rationale for the patent system—to promote the inefficiency of high monopoly prices because of the innovation it encourages. Thus, for the same reason that patents exist to promote innovation, CE criteria that implicitly limit the value of these patents should be modified to reflect the R&D incentives they induce. Technology adoption through cost-effectiveness is a price control policy in disguise, and may therefore have many of the properties of such policies.

At its core, CE analysis argues for technologies for which the static benefits to patients outweigh the costs, whether they are actual costs of production or, as more commonly used, the prices paid by consumers and/or public payers. CE analysis may be conducted at several levels and from different perspectives: for example, by health plans choosing technologies to be covered for their members or by nations financing care for their citizens. Since much of the controversy regarding pharmaceutical pricing has focused on national health care systems, our analysis is most pertinent to CE assessments conducted from the perspective of national payers, such as the UK's NICE.

In theory and presumably in practice, the benefits and costs used in such a CE analysis are incremental—that is, a given procedure improves health by one quality-adjusted life-year (QALY) at a price of $50,000 compared to a baseline therapy—the so-called standard of care or comparator technology. The benefit is the value of the additional quality-adjusted year of life, which comes at an additional cost of $50,000. Those technologies

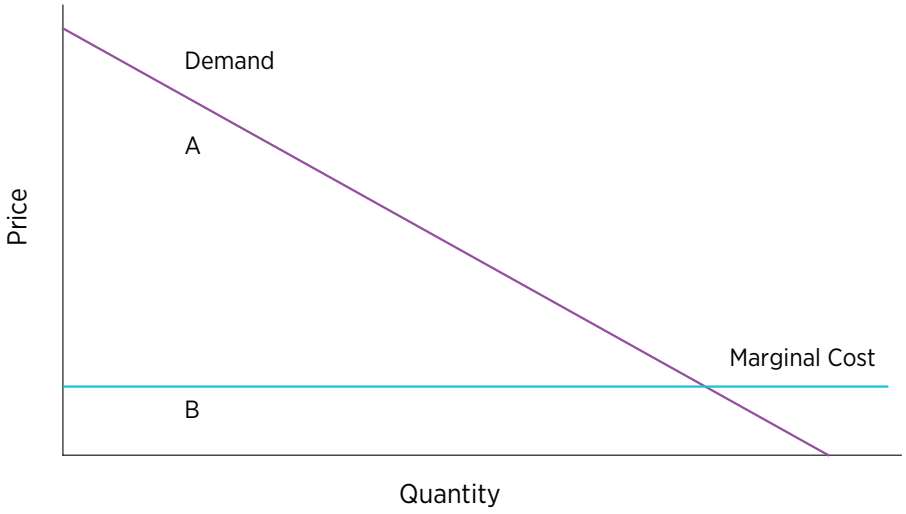
are deemed most cost-effective for which the incremental benefits far outweigh the additional costs to the health care system.

Translated into economic theory, we argue that technologies are most cost-effective when the associated consumer surplus—the benefits to consumers net of the price paid—is also large. Consumer surplus concerns the difference between benefits and costs, versus cost-effectiveness criteria which concerns the ratio. Figure 4 illustrates this concept with a standard diagram of supply and demand for a given drug therapy. As usual, the quantity of the drug is on the horizontal axis, while the price is on the vertical one.

The demand curve reflects society's willingness to pay for a given level of provision—its magnitude depends on several factors, one being the price (or availability) of other related technologies. For example, if the demand curve depicted the willingness to pay for loop diuretics, its height would depend on the price of substitute treatments, e.g., ACE inhibitors. The absence of good substitutes would result in a greater willingness to pay for diuretics, an outward shift in the demand curve. One can then interpret the demand curve for loop diuretics as identifying the incremental benefit of these drugs for a given price of alternative treatments.

The area under the demand curve (areas A+B) is the gross benefit to patients from consuming the drug. As more patients consume the drug, the gross benefit increases. The amount by which this benefit exceeds the price paid is the consumer surplus (area A) when the price paid equals the

Figure 4: Cost-Effectiveness in a Standard Model of Supply and Demand



marginal cost. We interpret the CE of this particular drug as the ratio of the gross incremental benefit to the total amount paid (A+B divided by B). The higher the gross benefit over the total amount paid, the higher the CE. The main implication of our analysis is that a drug's CE and consumer surplus are intimately related—the higher the consumer surplus, the higher the CE.

Figure 4 also depicts the supply curve for this drug. It is well known that the marginal costs of drug production are quite low, often on the order of cents per pill. The supply curve, here assumed to be flat, illustrates several points. First, if markets are competitive (price equals marginal cost), the net gains to consumers are large—area A in the figure. Both the consumer surplus and CE of the drug are high, primarily because the benefit to patients far outweighs the price paid by them. Moreover, the manufacturers of the drug make zero economic profits since the price of the drug equals its marginal cost. When markets are not competitive—as is commonly true of markets for new medical products—and producers charge prices that exceed marginal costs, the consumer surplus is lower and producers earn profits. The extent to which these profits compare to consumer surplus defines how the gains from innovation are divided.

We can now return to the question we started with: if the observed cost effectiveness of this drug were lowered, for example through higher prices paid by consumers, would current and future patients be worse off? More generally, what are the current and future implications of policies that limit health care spending growth, either through strict price controls or CE criteria that implicitly adopt only the most cost-effective technologies?

The answer to these questions depends on the process of drug discovery. *After a drug has been discovered*, economic theory tells us that society is best off if the price of the drug equals its marginal cost. The total quantity of drug supplied and consumed is at its highest, and drugs are only consumed by those whose benefit exceeds the cost of production. In this case, both consumer surplus and CE are high, and increases in price above marginal cost lower the welfare of current consumers.

In reality, drug discovery is an expensive ordeal, plagued by uncertainty in both the process of discovery and the ultimate effectiveness of the final product. When R&D is costly, companies require incentives to innovate, whether these incentives take the form of higher profits, subsidies for R&D, or some combination of the two. Higher profits come at a cost to current patients, health plans, and governments who pay higher prices. Higher profits, however, also stimulate innovation and are therefore beneficial to future patients.

This has the key implication that high levels of CE are often inconsistent with what economists commonly term "economic efficiency," defined by the highest level of access to therapy by both current and future

consumers. Figure 4 can be used to illustrate this with a simple, though extreme, example of perfect price discrimination. Suppose that a manufacturer can charge each patient their willingness to pay for (or benefit from) the drug—in this case, the gross benefit to patients remains the same but the net benefit or consumer surplus becomes zero. The manufacturer sells the drug at a price that exceeds its marginal cost and earns positive profits equal to the area A, the amount previously accruing to patients in the form of consumer surplus. The transfer of net benefits from patients to the manufacturer results in an observed CE that is minimized—the gross benefit to patients now equals the amount paid.

In this extreme example, economic efficiency is attained because access is maximized: current patients consume up to the point that the benefit equals the cost of production and future patients are ensured that firms have the largest incentive to innovate. The benefit to future patients of more innovative drugs comes at a cost to current patients who pay prices greater than the marginal cost of production. Importantly, this example illustrates that CE can be minimized when economic efficiency and access are maximized. Moreover, since all those whose benefit exceeds the cost of production actually purchase the drug, health is maximized. More generally, if companies are able to capture the full social benefit of their innovations, the likelihood of future drug discovery is highest. And although current patients may suffer from higher prices, the future sick may benefit from the innovative products that result from such profit incentives and that would otherwise not occur. In fact, this is the justification for the patent system which implicitly trades off the welfare of current and future consumers. Finally, while economists often make less distinction between consumers and producers than is seen in policy discussions, this distinction becomes less clear when patients themselves hold large stakes in companies and therefore benefit from increased profits, either directly as employees or indirectly through pension plans, mutual funds, and other investments in these very same companies.

International issues in patents and innovation

Perhaps because health care is primarily a local service industry, health economists have paid relatively little attention to international trade issues including international issues in patent regulations. However, it is well understood that medical R&D is driven by world returns, rather than returns from a given domestic market. For example, Swedish medical product firms innovate to sell worldwide, not just to the Swedish popula-

tion. Because world returns drive innovation and are central to health care spending growth, it follows that a given country's spending growth is driven by health care economies and policies of other countries. As such, spending growth in a small European country currently depends on how US policies affect world returns, just as future Medicare spending will depend on how emerging markets will affect those returns. However, health economists have conducted little explicit analysis on how health care policies in one country affect or should affect those of another.

In an attempt to bridge this gap, Egan and Philipson (2014) analyze the positive and normative implications of domestic IP and reimbursement policies when they affect global returns to innovation. The paper argues that IP and pricing of much of health care by domestic governments has some unique implications for determining world returns and the innovation it implies. In particular, the act of setting IP and reimbursement policies for providers and manufacturers, whether by allowing private pricing or through the generosity of public reimbursements, creates a public-goods problem in generating world returns to medical innovation. Taxation to fund the reimbursements and profits to the health care industry involves a private cost with a worldwide benefit through stimulating innovation. It follows directly that if medical innovation benefits all countries, a given country provides too little IP and under-reimburses providers and manufacturers as a result of its positive external effect on others. Thus, there will be too little medical innovation as it will not be sufficiently rewarded by world returns.

A key positive implication of this public-goods problem is that profit-provision through reimbursements in a given country is negatively correlated with the profit provision of other countries; that is, reimbursements will be so-called "strategic substitutes." A small European country may reimburse less generously because the United States reimburses more generously. An emerging economy may protect IP less because other countries protect it more. More precisely, the smaller the share of world demand and supply a country makes up, the less a government will protect IP and mark up prices above cost to promote innovation. Put differently, a small country has nothing to gain from protecting IP or raising its reimbursements, as it will see the same flow of new innovations regardless of what it does. In most markets, bigger buyers get lower prices. However, the free riding of providing world returns to innovation implies that these smaller European countries will have lower payments and reimbursements than the United States, despite the latter being the larger buyer. This may be reflected in lower European reimbursements for doctor and hospital services that cover innovations such as devices or drugs or for medical products directly through reference pricing or cost effectiveness thresh-

old policies.[4] Similarly, emerging markets that do not affect world returns much will not have an incentive to protect IP, until they become large enough that their own citizens suffer from a cut-back in world returns.

More precisely, consider when the amount of R&D affects the probability of discovery of a medical innovation according to P(R) where P(•) is increasing and concave. If $\Pi = \sum_{k=1}^{K} \pi_k$ are the world profits aggregated up over K countries, then the private R&D of the firm investing in medical innovation is that which maximizes expected profits as given by

$$R(\Pi) = argmax_R P(R)\Pi - R$$

This implies that the induced probability of discovery $P(\Pi) = P(R(\Pi))$ is increasing in world profits II.

Through IP protection or reimbursement policy, each country provides profits π_k and has its own welfare $w(\pi_k)$, which is decreasing in profit provision given the excess burden of the taxes financing reimbursements or due to standard monopoly distortions. Welfare decreases when a country must collect additional taxes in order to pay for higher priced drugs. Further, the excess burden of taxation would be included as a component of costs. The world expected social welfare across all countries is

$$\sum_{k=1}^{K} P(\Pi)\, w(\pi_k)$$

Within a given country, providing profits is a private bad that enables the public good of world returns to innovation. The socially efficient profit provision of each country therefore satisfies a classic public good condition that the private cost of raising reimbursement is equated to the value to the world of raising innovative returns

$$\sum_{k=1}^{K} P'(\Pi)\, w(\pi_k) = -P(\Pi)\, w'(\pi_k) \quad k = 1, 2, 3, \ldots K$$

This efficient provision of profits differs from the privately optimal (Nash equilibrium) provision that only takes into account how the country's costly profit provision affects its own welfare

$$P'(K\pi)\, w(\pi) = -P(K\pi)\, w'(\pi)$$

Thus, the private innovation benefit to a given country is smaller than the social benefit to all countries, so that world returns to medical innovation are under-provided by countries when acting in their own interest.

This public goods problem of providing world returns alters standard arguments about the classic effects of market size on innovation, which may involve how the growth of BRICS will alter medical innovation. In particu-

[4] Jena and Philipson (2008) discusses the implicit price controls that reimbursement based on cost effectiveness standards implies.

lar, the public goods problem may counteract the canonical positive effect that a growth of world markets has on innovative returns. To see this in its simplest form, consider when there are K homogeneous countries with the same domestic profits $\pi(K)$. An increase in the number of countries may be interpreted as the rise in "profitable" countries for which demand is above variable costs, such as, for example, the growth of world demand through the BRICS. The first order condition equating the marginal benefits and costs for the privately optimal level of profit provision in this case implies

$$P'\left(K\pi\right) w\left(\pi\right) = - P\left(K\pi\right) w'\left(\pi\right)$$

The optimal domestic behavior implies free riding in the sense that that domestic profits fall with the number of countries that contribute to world profits: $\frac{d\pi}{dK} < 0$. World returns are $\Pi = \pi(K)K$ and thus there are two effects of a growth in world market size on world returns

$$\frac{d\Pi}{dK} = \pi + \pi'(K)K$$

The first standard positive effect of market size on innovative returns is mitigated by the second negative effect induced by increased free riding when a larger group of countries provides the public good of medical innovation. In the extreme case, when the US or a single country is the only champion of medical innovative returns, K=1, world returns are efficient. As income growth in the BRICS makes them profitable for the innovation, K rises and the overall impact on world returns is a horse race between larger world markets and smaller US markups.

The empirical importance of these arguments stems from the large share of world returns occupied by a relatively small set of countries. Tables 1 and 2 summarize world health care and pharmaceutical expenditures for the largest countries. The health care expenditure, GDP, and population data come from the World Bank DataBank. Pharmaceutical expenditure data for OECD and BRICS countries is compiled from the OECD iLibrary and the National Health Accounts database at the World Health Organization[5] (WHO) respectively.[6] GDP and expenditure data for all of the countries are measured in constant US dollars (base year = 2000).

[5] I would like to thank Richard Liang at the WHO for giving me the BRICS pharmaceutical expenditure time series data.

[6] Note that I use the National Health Accounts and OECD data to compute pharmaceutical expenditure shares rather than the more commonly quoted IMS data. The IMS pharmaceutical data consists of "manufacturers sales to wholesalers and hospitals as well as retail sales of prescription medicine" (World Health Organization, 2004). The NHA and OECD data uses a broader definition of health care expenditures than IMS; for example IMS data does not include over-the-counter medicine sales. Consequently, the NHA data indicates higher pharmaceutical expenditure shares in developing countries than the IMS data.

Even though health economists often debate numbers such as the share of a country's GDP spent on health care, or total spending given per capita by income levels, what matters more for innovation incentives are aggregate world market shares, that is, what fraction of world returns a given country accounts for. Our data indicates that currently the United States remains the champion of both overall health care and pharmaceutical expenditures, accounting for about 50% of the world market share for health care and close to 40% of world pharmaceutical share. However, despite recent slowdowns, the projected surge in health care expenditures in BRICS and other countries may diminish this concentration in spending in the global health care economy.

Although health care spending in the US and other developed countries dominates the current level of spending in the BRICS countries, over the period 1995–2010, BRICS overall health care expenditures grew at twice the rate of the world health care expenditures. In terms of its share of total world health expenditures, growth in the BRICS countries has come not at the expense of the US, but at the expense of the other large countries (i.e., Japan, France, and Germany). As the BRICS country with both the largest overall health care sector and pharmaceutical sector, China is the driving force behind BRICS health care growth rates and spending levels. Despite similar population sizes, China spends four times as much on health care as India, and China's spending growth outpaced India's by 4.60%.[7]

Comparing Table 1 to Table 2 suggests that emerging economies devote a higher portion of total health expenditures to pharmaceuticals than do developed countries. BRICS health care spending is concentrated in pharmaceuticals with over 40% of total health expenditures spent on drugs in India and China compared to 12% in the US. As a result, the BRICS countries account for less than 8% of total world health expenditures but more than 15% of total world pharmaceutical expenditures. Thus, due to the relative size of their pharmaceutical markets, the BRICS countries may play a larger role in spurring the innovation of pharmaceuticals versus non-pharmaceutical medical products and the physician and hospital services tied to those products. However, the non-pharmaceutical related health care market in the BRICS countries is growing faster relative to the size of their pharmaceutical markets.

Despite recent slowdowns, future growth in world demand from the emerging markets of the BRICS will lower world concentration of aggregate demand and supply by making the United States less dominant. The arguments above predict that this will lead to lower US reimbursements

[7] Over the period 2005 through 2006, health care expenditures grew at an average annual rate of 12.88% and 8.28% in China and India respectively.

Table 1: World Health Care Expenditures

	Population (millions)		GDP Per Capita*		Income Share Spent on Health Care		Total Amt. Spent on Health Care* ($ billions)		Expenditure Share (% World Exp.)		World Rank (Expenditure Share)	
Country	2010	1995	2010	1995	2010	1995	2010	1995	2010	1995	2010	1995
United States	309	266	37,330	30,051	17.9%	13.6%	2,066	1,085	48.0%	45.0%	1	1
Japan	127	125	39,972	36,177	9.5%	6.9%	483	312	11.2%	13.0%	2	2
Germany	82	82	25,306	21,061	11.6%	10.1%	241	174	5.6%	7.2%	3	3
France	65	60	22,758	19,478	11.9%	10.4%	176	120	4.1%	5.0%	4	4
United Kingdom	62	58	28,034	20,724	9.6%	6.8%	168	82	3.9%	3.4%	5	5
China	1,338	1,205	2,426	658	5.1%	3.5%	165	28	3.8%	1.2%	6	10
Italy	60	57	18,943	17,671	9.5%	7.3%	109	73	2.5%	3.0%	7	6
Canada	34	29	25,575	20,170	11.3%	9.0%	99	54	2.3%	2.2%	8	7
Brazil	195	162	4,717	3,606	9.0%	6.7%	83	39	1.9%	1.6%	9	8
Spain	46	39	15,458	12,049	9.5%	7.4%	68	35	1.6%	1.5%	10	9
Korea, Rep.	49	45	16,219	9,548	6.9%	3.9%	56	17	1.3%	0.7%	11	17
Netherlands	17	15	26,553	20,429	11.9%	8.3%	53	26	1.2%	1.1%	12	11
Australia	22	18	25,249	18,627	8.7%	7.2%	49	24	1.1%	1.0%	13	12
Mexico	113	92	6,105	4,832	6.3%	5.1%	44	23	1.0%	1.0%	14	13
India	1,225	964	795	367	4.1%	4.3%	39	15	0.9%	0.6%	15	20
Russia	142	148	2,927	1,618	5.1%	5.3%	21	13	0.5%	0.5%	22	22
South Africa	50	39	3,753	2,960	8.9%	7.5%	17	9	0.4%	0.4%	27	25
World	6,894	5,715	6,006	4,788	10.4%	8.8%	4,301	2,410	100.0%	100.0%		

Notes:
*Measured in 2000 constant US Dollars.
GDP and population data come from the World Bank DataBank. Pharmaceutical expenditure data for OECD and BRICS countries is compiled from the OECD iLibrary and WHO National Health Accounts respectively.

Table 2: World Pharmaceutical Expenditures

	Population (millions)		GDP Per Capita*		Income Share Spent on Health Care		Share of Health Care Exp. Spent on Pharm.		Total Amt. Spent on Pharm.* (billions)		Expenditure Share** (% World Exp.)	
Country	**2008**	**1995**	**2008**	**1995**	**2008**	**1995**	**2008**	**1995**	**2008**	**1995**	**2008**	**1995**
United States	304	266	38,209	30,051	16.5%	13.6%	12.1%	8.4%	232	91	38.6%	30.1%
Japan	128	125	40,433	36,177	8.5%	6.9%	19.4%	22.2%	85	69	14.2%	22.9%
China	1,325	1,205	2,033	658	4.6%	3.5%	42.7%	54.2%	53	15	8.9%	5.0%
Germany	82	82	25,620	21,061	10.7%	10.1%	15.0%	12.8%	34	22	5.6%	7.3%
France	64	60	23,366	19,478	11.2%	10.4%	16.4%	15.0%	28	18	4.6%	6.0%
Italy	60	57	19,903	17,671	9.0%	7.3%	18.1%	20.7%	19	15	3.2%	5.0%
United Kingdom	61	58	29,107	20,724	8.9%	6.8%	11.8%	15.3%	19	13	3.1%	4.2%
Brazil	192	162	4,479	3,606	8.3%	6.7%	24.6%	16.7%	17	6	2.9%	2.1%
Canada	33	29	26,102	20,170	10.3%	9.0%	17.0%	13.9%	15	7	2.5%	2.5%
India	1,191	964	689	367	4.0%	4.3%	44.2%	55.4%	15	8	2.4%	2.8%
Spain	46	39	16,251	12,049	9.0%	7.4%	18.7%	19.2%	12	7	2.1%	2.2%
Mexico	111	92	6,327	4,832	5.9%	5.1%	28.3%	#N/A	12	0	1.9%	0.0%
Korea, Rep.	49	45	15,350	9,548	6.5%	3.9%	23.2%	23.6%	11	4	1.9%	1.3%
Australia	21	18	25,246	18,627	8.7%	7.2%	14.6%	12.2%	7	3	1.2%	1.0%
Belgium	11	10	25,100	19,940	10.0%	8.5%	16.4%	18.1%	4	3	0.7%	1.0%
South Africa	49	39	3,796	2,960	8.6%	7.5%	25.1%	28.3%	4	2	0.7%	0.8%
Russia	142	148	3,044	1,618	4.8%	5.3%	18.8%	18.9%	4	2	0.7%	0.8%
World	6,737	5,715	6,026	4,788	9.8%	8.8%	#N/A	#N/A	601	302	100.0%	100.0%

Notes:
*Measured in 2000 constant US Dollars.
**World totals calculated using all available data which is limited to BRICS and OECD countries.
GDP and population data come from the World Bank DataBank.
Pharmaceutical expenditure data for OECD and BRICS countries is compiled from the OECD iLibrary and WHO National Health Accounts respectively.

when it loses its dominant role in world returns. In general, growth in world markets may have two offsetting effects on innovation: the standard positive effect from an increase in world market size, and the offsetting negative effect due to increased free riding when world concentration in health care falls.

A back-of-the-envelope calculation illustrates that the markup reductions in the United States and other countries do not have to be large to offset predicted growth rates in demand from the BRICS. Currently, the BRICS contribute approximately 7% to world spending in health care. If by current industry estimates, such as that of IMS Health,[8] their spending grows by 20% in the next three years, they would still make up only about 8.28% of world spending. This implies that a decrease in markups of only 1.5% in non-BRICS countries would be enough to offset this 20% growth from BRICS. The small reduction in markups needed to offset the substantial spending growth from the BRICS is due to the substantial concentration in world health care spending. Our estimates of the size of the strategic substitutability in reimbursements suggest that under reasonable conditions, when world concentration of health care supply and demand falls, the growth in BRICS market size may lower medical innovation returns as a result of declines in reimbursements in the United States and other rich countries.

The overall point of considering international linkages is that they greatly alter positive and normative analyses of domestic IP and reimbursement policies. On a positive level, these linkages seem to be important for explaining differences in European and US reimbursement policies—and hence spending differences—and to explain the lack of IP protection in emerging economies with small world market shares. On a normative level, they are important for evaluating the effects and desirability of domestic health care reforms aimed at curbing domestic spending growth resulting from world returns.

Conclusion

This chapter discusses recent research on the unique aspects of patents as they relate to innovation for medical products. We argue that the presence of substantial marketing affects the trade-offs of patents, that common forms of central pricing of these products do not have their intended effects when patent monopolists act in their own interest, and that international aspects of central pricing of health care greatly alters the effects

[8] This is the suggested growth rate in industry publications, see e.g. IMS Institute's *The Global Use of Medicines Outlook through 2016*.

and evaluation of domestic intellectual property policies. Overall, we argue that these unique issues with medical products have an impact on how effective patents are in promoting medical innovation and how the desirability of specific intellectual property policies should be evaluated.

References

Bethan, G., A. Harris, and A. Mitchell (2001). Cost-effectiveness analysis and the consistency of decision making: Evidence from pharmaceutical reimbursement in Australia (1991–1996). *PharmacoEconomics* 19(11): 1103–1109.

Drummond, M., B. O'Brien, G. Stoddart, and G. Torrance (1997). *Methods for the Economic Evaluation of Health Care Programmes.* Oxford University Press.

Egan, M., and T. Philipson (2013). *International Health Economics*. National Bureau of Economic Research Working Paper Series (No. 19280). <http://www.nber.org/papers/w19280>, as of August 3, 2016.

Gabszewicz, J.J., and X.Y. Wauthy (2002). Quality underprovision by a monopolist when quality is not costly. *Economics Letters* 77(1): 65–72.

Garber, A., and C. Phelps (1997). Economic foundations of cost-effectiveness analysis. *Journal of Health Economics* 16(1): 1–32.

Gold, M., J. Siegel, L. Russell, and M. Weinstein (1996). *Cost-Effectiveness in Health and Medicine*. Oxford University Press.

Goldman, D., and D. Lakdawalla (2011). Chapter 13: Intellectual property, information technology, biomedical research, and marketing of patented products. In Mark V. Pauly, Thomas G. Mcguire, and Pedro P. Barros (eds.). *Handbook of Health Economics* (Elsevier): 825–872.

IMS Institute for Healthcare Informatics (2012). *The Global Use of Medicines: Outlook through 2016.* IMS Institute for Healthcare Informatics.

Jena, A., and T. Philipson (2008). Cost-effectiveness analysis and innovation. *Journal of Health Economics* 27(5): 1224–1236.

Lakdawalla, D., and T. Philipson (2012). Does intellectual property restrict output? An analysis of pharmaceutical markets. *The Journal of Law & Economics* 55(1): 151–187.

Malani, A., and T. Philipson (2012). The regulation of medical products. In Patricia M. Danzon and Sean Nicholson (eds.). *The Oxford Handbook of the Economics of the Biopharmaceutical Industry.* Oxford University Press.

Mussa, M., and S. Rosen (1978). Monopoly and product quality. *Journal of Economic Theory* 18(2): 301–317.

Newhouse, J. (1992). Medical care costs: How much welfare loss? *Journal of Economic Perspectives* 6(3): 3–21.

Nordhaus, W.D. (1969). *Invention, Growth, and Welfare: A Theoretical Treatment of Technological Change*. MIT Press.

US Dept. of Commerce (2004). *Pharmaceutical Price Controls in OECD Countries: Implications for U.S. Consumers, Pricing, Research and Development, and Innovation*. United States Government, Dept. of Commerce.

About the authors

Steven Globerman

Steven Globerman is the Kaiser Professor of International Business at Western Washington University in the College of Business and Economics, and a Fraser Institute senior fellow. He has published more than 150 articles and monographs and is the author of the book, *The Impacts of 9/11 on Canada-U.S. Trade*, as well as a textbook on international business management. In the early 1990s, he was responsible for coordinating Fraser Institute research on the North American Free Trade Agreement. In addition, Dr. Globerman has served as a researcher for two Canadian Royal Commissions on the economy as well as a research advisor to Investment Canada on the subject of foreign direct investment. He earned his B.A. in economics from Brooklyn College, his M.A. from the University of California, Los Angeles, and his Ph.D. from New York University.

Kristina M. Lybecker

Kristina M. Lybecker is an Associate Professor of Economics in the Department of Economics and Business at Colorado College in Colorado Springs, CO. She received her Ph.D. in Economics in 2000 from the University of California, Berkeley. Prof. Lybecker's research analyzes the difficulties of strengthening intellectual property rights protection in developing countries, specifically in the context of the pharmaceutical and environmental technology industries. Her recent publications have also addressed alternatives to the existing patent system, the balance between pharmaceutical patent protection and access to essential medicines, and the markets for jointly produced goods such as blood and blood products, and the role of international trade agreements in providing incentives for innovation. Prof. Lybecker has testified in more than a dozen states on the economics of pharmaceutical counterfeiting. In 2016 she was awarded the Thomas Edison Innovation Fellowship by the Center for the Protection of Intellectual Property (CPIP) at George Mason University School of Law.

She has also worked with the US Food and Drug Administration, Reconnaissance International, PhRMA, the National Peace Foundation, the OECD, the Fraser Institute, and the World Bank, on issues of innovation, international trade, and corruption.

Christopher Sands

Christopher Sands is Senior Research Professor at the Paul H. Nitze School of Advanced International Studies of Johns Hopkins University where he is also the Director of the Center for Canadian Studies. Concurrently he serves as the G. Robert Ross Distinguished Visiting Professor in the College of Business and Economics at Western Washington University and as a non-resident Senior Associate of the Center for Strategic and International Studies.

Tomas J. Philipson

Tomas J. Philipson, Ph.D, is an economist who holds the Daniel Levin Chair in Public Policy at the University of Chicago and directs The Becker Friedman Institute's health care research program. In addition, he is a co-founder of the health care consulting firm Precision Health Economics, a Visiting Scholar at the American Enterprise Institute, and a Senior Fellow at the Milken Institute. Dr. Philipson has served in the US government as a senior economic adviser to the head of the Food and Drug Administration (FDA), a senior economic adviser to the head of the Centers for Medicaid and Medicare Services (CMS), and a senior health care adviser to Senator John McCain during his 2008 presidential campaign. He received his MA and PhD in economics from the Wharton School and the University of Pennsylvania.

Acknowledgments

The authors would like to thank the anonymous reviewers for comments on earlier drafts of these chapters. Any remaining errors or oversights are the sole responsibility of each author. The views and conclusions expressed in this book do not necessarily reflect those of the Board of Directors of the Fraser Institute, the staff, or supporters.

Publishing information

Distribution

These publications are available from <http://www.fraserinstitute.org> in Portable Document Format (PDF) and can be read with Adobe Acrobat® or Adobe Reader®, versions 7 or later. Adobe Reader® XI, the most recent version, is available free of charge from Adobe Systems Inc. at <http://get.adobe.com/reader/>. Readers having trouble viewing or printing our PDF files using applications from other manufacturers (e.g., Apple's Preview) should use Reader® or Acrobat®.

Ordering publications

To order printed publications from the Fraser Institute, please contact:

- e-mail: sales@fraserinstitute.org
- telephone: 604.688.0221 ext. 580 or, toll free, 1.800.665.3558 ext. 580
- fax: 604.688.8539.

Media

For media enquiries, please contact our communications department at 604.714.4582 or via e-mail at communications@fraserinstitute.org. In Toronto, contact our media specialist at 416.363.6575, ext. 238.

Copyright

Date of issue

2016

ISBN

978-0-88975-417-1

Citation

Globerman, Steven (ed) (2016). *Intellectual Property Rights and the Promotion of Biologics, Medical Devices, and Trade in Pharmaceuticals.* Fraser Institute. <http://www.fraserinstitute.org>.

Supporting the Fraser Institute

To learn how to support the Fraser Institute, please contact

- Development Department, Fraser Institute
  Fourth Floor, 1770 Burrard Street
  Vancouver, British Columbia, V6J 3G7 Canada
- telephone, toll-free: 1.800.665.3558 ext. 586
- e-mail: development@fraserinstitute.org
- website: <http://www.fraserinstitute.org/support-us/overview.aspx>

Purpose, funding, and independence

The Fraser Institute provides a useful public service. We report objective information about the economic and social effects of current public policies, and we offer evidence-based research and education about policy options that can improve the quality of life.

The Institute is a non-profit organization. Our activities are funded by charitable donations, unrestricted grants, ticket sales, and sponsorships from events, the licensing of products for public distribution, and the sale of publications.

All research is subject to rigorous review by external experts, and is conducted and published separately from the Institute's Board of Trustees and its donors.

The opinions expressed by authors are their own, and do not necessarily reflect those of the Institute, its Board of Trustees, its donors and supporters, or its staff. This publication in no way implies that the Fraser Institute, its trustees, or staff are in favour of, or oppose the passage of, any bill; or that they support or oppose any particular political party or candidate.

As a healthy part of public discussion among fellow citizens who desire to improve the lives of people through better public policy, the Institute welcomes evidence-focused scrutiny of the research we publish, including verification of data sources, replication of analytical methods, and intelligent debate about the practical effects of policy recommendations.

About the Fraser Institute

Our mission is to improve the quality of life for Canadians, their families, and future generations by studying, measuring, and broadly communicating the effects of government policies, entrepreneurship, and choice on their well-being.

Notre mission consiste à améliorer la qualité de vie des Canadiens et des générations à venir en étudiant, en mesurant et en diffusant les effets des politiques gouvernementales, de l'entrepreneuriat et des choix sur leur bien-être.

Peer review—validating the accuracy of our research

The Fraser Institute maintains a rigorous peer review process for its research. New research, major research projects, and substantively modified research conducted by the Fraser Institute are reviewed by experts with a recognized expertise in the topic area being addressed. Whenever possible, external review is a blind process. Updates to previously reviewed research or new editions of previously reviewed research are not reviewed unless the update includes substantive or material changes in the methodology.

The review process is overseen by the directors of the Institute's research departments who are responsible for ensuring all research published by the Institute passes through the appropriate peer review. If a dispute about the recommendations of the reviewers should arise during the Institute's peer review process, the Institute has an Editorial Advisory Board, a panel of scholars from Canada, the United States, and Europe to whom it can turn for help in resolving the dispute.

Editorial Advisory Board