BIOSIMILARS: THE QUEST FOR A RATIONAL REGULATORY AND INTELLECTUAL PROPERTY APPROACH IN CANADA

by

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One's life, when blessed with good fortune, is not lived in isolation. It is a product of love, friendship, and judiciously dispensed hard-truths. It gives me great pleasure to recognize those who have so contributed and enduringly supported me academically, professionally, and most important, personally in all my achievements.

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ABSTRACT

Biologics and biosimilars represent the promise for more effective treatments of many diseases. International treaty obligations influenced heavily by the biopharmaceutical industry and advanced through the international trade agenda may lead to an imbalance between incentivizing innovation and the public interest. Canada's implementation of its obligations into national patent and regulatory laws encourages aggressive biologic patent protection strategies that, coupled with linked regulatory assessments, may establish compounding layers of exclusion that disproportionately disincentivizes both the biologics innovation and biosimilar development. This comparative analysis addresses the progression of international obligations and the way in which they have been implemented into Canada's patent/IP and regulatory frameworks as compared to the US and EU. A quantitative comparison of biosimilar approvals and launches provides insight on how international obligations and national legislation have impacted these outcomes. Patent and regulatory laws must be balanced to incentivize innovation and promote access to treatments now and tomorrow.

LIST OF ABBREVIATIONS USED

BLA	Biologics License Application
CDER	Center for Drug Evaluation and Research
EMA	European Medicines Agency
US FDA	US Food and Drug Administration
NDA	US New Drug Application
NDS	Canadian New Drug Submission

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I am grateful for the opportunity to embark on this endeavour and would like to acknowledge the perspective that my professional experience brings to this research. For the better part of two decades I have been engaged in private practice concerning the identification, acquisition, management and enforcement of intangible assets and intellectual property rights in different industries including in the biopharmaceutical industry. The majority of my early career, even prior to my licensure, was predominately pharmaceutical patent litigation, first brand and then generic, and life cycle management.

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CHAPTER 1. Introduction

This work is an exploration of Canada's regulation of biosimilars and its integration with Canadian intellectual property laws. Specifically, this work explores the evolution and impact that the national implementation of Canada's international obligations has had on the approval and market availability of biosimilars in Canada in comparison to the US and EU. Essentially, it studies the question of how Canada's translation of its international treaty obligations into its national legislative and regulatory framework has affected biosimilar authorizations and market launches given that these obligations were initially framed in the pharmaceutical context and promulgated through the international trade agenda apparatus. This work therefore is an examination of how international treaty obligations related to the regulation and protection of pharmaceuticals and biologics have become more stringent over time and linked to patent and IP considerations as a result of the influence of powerful countries like the US and EU and their equally powerful pharmaceutical industries, and how Canada's chosen modes for the implementation of these treaty obligations have affected the approval and market launch of biosimilars in comparison to the US and EU.

1.1. Problem

With rapid advancements over the last few decades, the emergence of a new class of complex therapeutic products, namely biologics, is causing technological, medical, economic and legal ripples across the globe. Biologics hold the potential to expand the frontiers of medical treatments for the betterment of global public health.[1] This emerging class of therapeutics is especially important in the development of treatments for chronic and often disabling conditions such as diabetes, autoimmune diseases and

[1] B. Leader, et al., *Protein therapeutics: a summary and pharmacological classification*, 7 NAT REV DRUG DISCOV (2008). T. Liu, *Natural and biotech-derived therapeutic proteins: What is the future?*, 21 ELECTROPHORESIS (2000).

cancer, the treatments of which are beyond the capabilities of existing pharmaceutical drugs.[2]

However, biologics are increasingly becoming enormously expensive; the Patent Medicines Prices Review Board[3] reported that that in a decade the sales of biologics in Canada has tripled[4] and number of patented biologics costing at least $10,000 annually made up $5.4B of the $7.7B in Canadian biologics sales in 2018.[5] As well, biologics are complicated, time consuming and expensive to produce all of which contributes to making the costs of these treatments equally exorbitant.[6] Indeed, the economic impact of the biologics industry is staggering given that this class of therapeutics barely existed 30 years ago. The global biologics market for 2019 has been pegged at USD$255B and is estimated to grow to USD$457B by 2027.[7] Accordingly, it is important to strike the appropriate balance to achieve the overall goal of promote innovation of new biologics while providing conditions to encourage biosimilar competition in order to manage the prices pressures on patients and payers.[8]

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[2] D. C. Ohly & S. K. Patel, *There is no Orange Book: the coming wave of biological therapeutics*, 6 JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE 464(2011). Health Canada, *Biosimilar biologic drugs in Canada: Fact Sheet - Canada.ca*(2016), *available at* https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html. United States of America, Biosimilar Action Plan: Balancing Innovation and Competition 1 (Food and Drug Administration ed., 2018). European Medicines Agency, *Biosimilars medicines: Overview*(2020), *available at* https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview. Food and Drug Administration, *Biosimilar and Interchangeable Products | FDA*, @US_FDA(2020), *available at* https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products.

[3] Established by the Canadian Parliament in 1987, the Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial body with a dual regulatory and reporting mandate. First, to ensure that prices at which patentees sell their patented medicines in Canada are not excessive, and second, to report on pharmaceutical trends of all medicines and on research and development spending by patentees.

[4] Government of Canada, Biologics in Canada Part 1: Market Trends, 2018 6 (Patented Medicines Prices Review Board ed., 2018).

[5] Id. at, 15.

[6] Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Future of Competition in the Biologics Market*, 31 TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW (2012).

[7] CMI, *Global Biologics Market to surpass US$ 456.83 8 Billion by 2027, Says CMI*, Coherent Market Insights(April 3, 2020), *available at* https://www.globenewswire.com/news-release/2020/04/03/2011472/0/en/Global-Biologics-Market-to-surpass-US-456-83-8-Billion-by-2027-Says-CMI.html.

[8] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).

But, what exactly is a biologic? Often characterized as protein-based drugs, they are therapeutic agents that can be used to treat medical conditions that have previously been inefficiently managed, or not treated at all because pharmaceuticals were not capable of doing so efficiently, or doing so at all.[9] Biologics are manufactured using complex recombinant technology using, containing and/or derived from biological sources such as living organisms including bacteria, yeast, mammal cells and enzymes.[10]

Pharmaceuticals differ from biologics in very critical ways; they are small molecules that have generally been identified through a trial-and-error approach with biological function determined through various biological assays for activities that are, in comparison, more simple than the methods that are required to determine the efficacy of biologics. Pharmaceuticals are generally not structurally complex, capable of being manufactured on an industrial scale, and are comparably thermo- and chemically stable.[11]

For instance, Tylenol® is Johnson & Johnson's branded product containing the active pharmaceutical ingredient acetaminophen; it has been used for over a century and is the most commonly used medication for pain and fever in both the US and EU.[12] Acetaminophen is small in size ($C_8H_9NO_2$ – just 20 atoms), very stable in a solid form at room temperature and well above.[13] The manufacturing process for acetaminophen is chemically simple and is produced on an industrial scale. Insulin, on the other hand, is one of the first biologics granted market authorization in the early 80s, not particularly

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[9] Wilkinson Michael Kleinberg & Wilkinson Kristen Mosdell, *Current and future considerations for the new classes of biologicals*, 61 AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY (2004). E. Philip Johnson, *Implications of biosimilars for the future*, 65 see id. at (2008). Matthew J. Seamon, *Antitrust and the biopharmaceutical industry: lessons from Hatch-Waxman and an early evaluation of the Biologics Price Competition and Innovation Act of 2009*, 34 NOVA LAW REVIEW 629(2010).

[10] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004). Johnson, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2008).

[11] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004). Johnson, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2008).

[12] RICHARD J. PRANKERD, CRITICAL COMPILATION OF pK_A VALUES FOR PHARMACEUTICAL SUBSTANCES § 33 (Harry G. Brittain ed., Elsevier. 2007).

[13] E. Kalatzis, *Reactions of acetaminophen in pharmaceutical dosage forms: its proposed acetylation by acetylsalicylic acid*, 59 J PHARM SCI (1970).

complex in comparison to more recently developed biologics. And yet this relatively simple biologic is 250-fold larger than acetaminophen and degrades in less than a month at room temperature and in minutes in extreme heat or with prolonged exposure to sunlight.[14]

Biologics are a different beast. Unlike small-molecule pharmaceuticals, biologics are macromolecules of greater complexity which heavily influence the production process. Cellular systems, protein composition and concentration, temperature, amino acid arrangement and folding, and molecular weight all affect the final product.[15] Thus and unlike pharmaceuticals, the concept of a "generic" biologic is untenable as a result of these fundamental biological and chemical differences. Instead, various descriptors have been coined, such as "follow-on biologic", "biosimilar", "second-entry biologic", and "subsequent-entry biologics" ("SEB" or "biosimilar") which describes a biologic that is highly similar to and has no clinically meaningful differences from a previously authorized biologic.[16]

In an American study in 2019, a survey of employers found that although biologics accounted for only 1% of all prescriptions dispensed to their workers and dependents, they accounted for 40% of all monies spent for drugs.[17] Thus, stakeholders such as patients and public and private payers (governments and insurance companies) are motivated to seek ways to reduce these high costs and promote widespread use of these exceptional treatments to benefit Canadians. One area of particular interest to achieve this goal is the strategy to promote the efficient approval and adoption of biosimilars in Canada; the prevailing thinking is that biosimilars will exert downward

[14] PRANKERD. 2007.
[15] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004).
[16] Canada. 2016. Agency. 2020. Administration. 2020.
[17] Willis Towers Watson, *Leading employers spend 40% of costs on less than 1% of prescriptions* (August 20, 2019), *available at* https://www.willistowerswatson.com/en-US/News/2019/08/leading-employers-spend-40-percent-of-costs-on-less-than-1-percent-of-prescriptions. America, 1. 2018.

pressure on the price of biologics as a result of increased competition which was a net result in the analogous brand/generic pharmaceutical context.[18]

Ultimately, however, the true potential of biologics and biosimilars may not be fully realized where there is imbalance between the following factors that may, to varying degrees, impede their development:

- patent and intellectual property interests of biologics and biosimilar developers and manufacturers;
- regulatory framework for the market authorization process;
- commercialization and integration into both the public and private payer markets;
- public and/or private incentivization of R&D efforts; and
- public health policy.

International treaty obligations related to the first two factors play a significant role in the development of regulatory regimes around the world, including their linkages to patent and IP considerations prior to a biosimilar's grant of market authorization. The greatest impact on the adoption and authorization of biologics and biosimilars is the way Canada has crafted its international obligations at the national level.

Finally, one might speculate whether Canada would have made the same choices and implemented its national frameworks in respect of pharmaceuticals and biologics in the same way absent pressure from trading partners and powerful multi-national industry players.

[18] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012). Government of Canada, Biologics in Canada Part 2: Biosimilar Savings, 2018 6 (Patented Medicines Prices Review Board ed., 2018). Elena Lungu, Biosimilar in Canada: Current Environemtna and Future Opportunity (Patented Medicines Prices Review Board ed., 2019).

1.2. Research Question and Methodology

In the context of the problem set out above, the research question that this work explores and seeks to answer is as follows:

> HOW HAS THE APPROVAL AND LAUNCH OF BIOSIMILARS IN CANADA BEEN IMPACTED BY THE EVOLUTION OF NATIONAL LEGISLATION LINKING BIOSIMILAR REGULATION WITH PATENT/IP CONSIDERATIONS AS MANDATED BY THE PROGRESSION OF CANADA'S INTERNATIONAL TREATY OBLIGATIONS, IN COMPARISON TO THE US AND EU?

In order to answer this question, the following methodology will be applied to this research delving into: (1) an analysis of the evolution of international treaty obligations; (2) a comparison of the way in which Canada, as compared to the US and EU, has chosen implement these treaty mandates in its national patent and regulatory framework; (3) a quantitative analysis of biosimilars approved and launched in Canada, as compared to the US and EU; and (4) an evaluation of whether and how the measurable differences in biosimilar approval and launch may be attributable to Canada's treaty obligations and/or the way in which these obligations were implemented in its national legislation.

However, understanding how the approval and launch of biosimilars in Canada has been impacted by its national legislative implementation of its international obligations first requires an appropriate foundation upon which to build. This foundation is a description of the biologics/biosimilars industry and technological realities, the similarities in the regulation of biologics and biosimilars across Canada, the US and EU, as well as the harmonization of patent laws and coordination of patent strategies. These concepts are the necessary underpinnings to give appropriate context to the progression of international treaty obligations as they relate to the regulation of biologics and biosimilars and a comparative analysis of the national implementation of those international obligations in Canada, the US and EU.

The industry and technological realities, touched on in Section 1.1 and addressed in further detail in Chapter 2, affect the regulation and protection of biologics. Each of Canada, the US and EU have sophisticated and comprehensive laws, regulations and agencies that regulate biologics and biosimilars.[19] These same bodies – the US' Food and Drug Administration (FDA), EU's European Medicines Agency (EMA) and Canada's Health Canada – are the same governmental agencies that also regulate brand and generic pharmaceuticals. These regulatory efforts are ostensibly governed by each state independently; practically, however, there is significant international integration of standards and even reliance between these regulatory agencies. The regulatory principles applicable to biologics/biosimilars – by and large founded upon the regulatory principles for pharmaceuticals – are common among Canada, the US and EU and focus on the safety, efficacy and quality.[20] In the case of the research at hand, the important aspect of the regulatory pathways in Canada, the US and EU is not their differences, but rather it is the commonality in the way that each of their regulatory processes are designed to similarly interact with the patent/IP clearance measures mandated by their international obligations. For instance: while there are differences in the patent linkage systems between Canada and the US, the regulatory triggering events, i.e., a biosimilar approval that may be required to be stayed until the status of patent rights has been litigated, are the same.

In terms of the harmonization of patent laws, international treaties have encouraged the adoption of a baseline commonality of patent laws such as eligibility requirements – novelty, utility, non-obviousness and subject matter – while making modest concessions for some variability such as accommodation for codified morality or ethical considerations. Certainly, the Patent Cooperation Treaty and its continuing efforts for signatories to harmonize and streamline the patent prosecution process prior to

[19] Michael S. Montgomery, *Generics And Biosimilars: Mapping The Biosimilars Regulatory Approval Pathway Against The Hatch-Waxman Act And Projecting Futures Effects On The Biologics Market And Patent Protection*, 75 UNIVERSITY OF PITTSBURGH LAW REVIEW (2015).
[20] Jason Kanter & Robin Feldman, *Understanding the Incentivizing Biosimilars*, 64 HASTINGS LAW JOURNAL, 60, 63 (2012).

National Phase has gone a long way in facilitating industry's ability to globally strategize and manage its portfolio.

Prior to the commencing the main analysis, some historical context is also warranted given Canada's complicated history with the pharmaceutical industry. For the better part of the 20th century, Canada was the home of a burgeoning generic pharmaceuticals industry relying on a "compulsory licensing" model that forced brand pharmaceutical companies to license its patented inventions to generic manufacturers for low and set licensing royalties. Generic manufacturers would then manufacture lower cost generics in Canada without contravening any Canadian patent laws, then sell their products in other countries. This practice was effectively halted in the early 90s through the coercive efforts of the US, EU and their brand pharmaceutical industries through the international trade agenda.

With that foundation set, the first matter in order to address the research question is an examination of international treaties and free trade agreements to which Canada, as well as the US and EU, is obligated (as they relate to the regulation and patenting of biologics and biosimilars), including a review of how these obligations have evolved, as will become evident, in an increasingly stringent manner. Over time and as a result of industry efforts, various international treaties and obligations have incrementally created obligations on signatories like Canada to, instead of compulsory licensing, adopt domestic laws (1) linking the regulatory authorization of a biosimilar to the status of existing patents related to an analogous biologic ("patent linkage") (2) carving out periods where an biosimilar applicant is precluded from relying on the data of a previously authorized biologic ("data exclusivity") and (3) other patent and/or intellectual property-based considerations including patent term extensions or restorations, patent re-examinations and reissuance entitlements and "supplemental" protections that are not tied to patents or data ("additional IP provisions").

The advancement of provisions crafted to protect pharmaceuticals spread through the international trade agenda that was first multilaterally enshrined in the *Agreement of*

Trade-Related Aspects of Intellectual Property Rights,[21] (TRIPs). TRIPs was the first treaty to mandate the adoption of data exclusivity legislation and sought to bring harmony to patent laws among signatory countries.[22] Prior to TRIPs, Canada entered into the *North American Free Trade Agreement*,[23] where the US first obliged Canada to adopt statutory data exclusivity and harmonize its patent laws to standards set out therein. Recently renegotiated and replacing North American FTA (1992), the *Canada-US-Mexico Free Trade Agreement*,[24] imposes tightened patent linkage requirements, increased data exclusivity thresholds and introduces the concept of a *sui generis rights* regime, all of which was already mandated by the EU arising from the *Comprehensive and Economic Trade Agreement*.[25] Negotiations were concurrently underway on the *Trans-Pacific Partnership* which did not enter into force due to the US' refusal to ratify the agreement; the subsequently enacted *Comprehensive and Progressive Agreement for Trans-Pacific Partnership*[26] that rose from the ashes of the TPP was the basis for significant amendment to Canada's patent linkage regime, but provisions related to data exclusivity and *sui generis* rights remain suspended but not potentially reinstable.

After the international context has been established, a comparative analysis is undertaken to examine how each of Canada, the US and EU crafted their national legislative and regulatory frameworks related to the regulation and protection of biologics and biosimilars; in essence, this is an examination of how their international obligations have been practically implemented. Treaty obligations relating to the regulation of biologics and biosimilars mandate, either directly or indirectly, the national

[21] Agreement On Trade-Related Aspects Of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994). TRIPS was negotiated during the Uruguay Round trade negotiations of the General Agreement on Tariffs and Trade (GATT) from 1986 to 1994. As an agreement of the World Trade Organization (WTO), TRIPS is legally binding for all WTO Member states. Also at the Uruguay Round, the Council for TRIPS was created to monitor the operation of the agreement and governments' compliance.
[22] Id. at, Article 39.3.
[23] North American Free Trade Agreement, 17 December 1992, Can. T.S. 1994 No. 2, 32 I.L.M. 289 (entered into force 1 January 1994).
[24] Canada US Mexico Free Trade Agreement (2020).
[25] Comprehensive and Economic Trade Agreement (2017). ("Canada- FTA (2017)").
[26] Comprehensive and Progressive Agreement for Trans-Pacific Partnership. (2018). ("CPTPP (2018)").

adoption of patent linkages, data exclusivity and additional IP provisions, but exact implementation of this mandate is at the discretion of the signatory state. For example, the US was an early adopter of a patent linkage regime established by the Drug Prices Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act")[27] in 1984 which manifested as an *in rem* action[28] forum for pharmaceutical patent litigation. Canada followed suit in 1993 with the creation of their patent linkage regime through the Canadian *Patent Act*[29] and *Patented Medicines (Notice of Compliance) Regulations*.[30] As will become evident, not all implementation strategies were created equal.

Finally, a quantitative analysis of the number of biosimilars approved and launched in each of Canada, the US and the EU is undertaken as a measure of the success of their respective national regulatory and patent frameworks and to gain further insight into the effect that their respective underlying international obligations have had at the national level. By way of measurement, we will then determine if there is a difference in the approval and launch of biosimilars between Canada as compared to the US and EU. There is an important distinction to be mindful of in this assessment, namely approval versus launch or availability on the market. Based on any ascertained quantitative differences, an analysis of whether these differences arise from either the international obligations as they have progressed over time, or the way in which the national legislative and regulatory frameworks have been crafted by Canada, in comparison to the US and EU.

The choice to use the US and EU as comparison jurisdictions is based on a number of factors, the first of which is due to their respective economic importance as the first and third largest markets for biologics and biosimilars.[31]

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[27] Drug Price Competition and Patent Term Restoration Act of 1984 Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified across various provisions of Titles 21 and 35 of the U.S. Code).
[28] Meaning any judgement arising from an in rem action applies across the jurisdiction in contrast to *in personam* judgements that bind only the parties to the proceeding.
[29] Patent Act, R.S.C., 1985, c. P-4.
[30] Patented Medicines (Notice of Compliance) Regulations, SOR/93-133.
[31] Grand View Research, *Biologics Market Size Forecast - Industry Growth Report, 2018-2025*.

Second, there is a high degree of overlap in terms of the similar language contained in international treaties to which the US, EU, and Canada are signatories. Canada and the US are signatories to the *Canada-US-Mexico Free Trade Agreement* and, up until the US' withdrawal, the *Trans-Pacific Partnership*. Canada and the EU are signatories to the *Comprehensive and Economic Trade Agreement*. All parties are signatories to TRIPs.

Third, there is a high degree of commonality in the regulation of biologics and biosimilars in each of jurisdiction, EU historically being on the leading edge of the regulation of biologics and biosimilars. This means that the operation of the treaty mandated patent linkages, data exclusivity and additional IP provisions will be implemented in concert with regulatory pathways that look the generally the same in each jurisdiction.

Fourth, there is a high correlation between the location of innovative companies, historically clustered in the US and EU, involved in the R&D of therapeutics to where they will initially seek patent protection and market authorization.[32] Not all efforts to get drugs approved are made equally across the globe; a company is more likely to advance a patent strategy in the US and EU first, then the will seek patents next in economically important jurisdictions where there is commercial activity such as Canada.[33]

Choosing the US and EU as comparators will mitigate the influence of additional factors, (such as different market strategies, local partnership/development strategies, secondary market patent strategies) that may come into play when companies decide to seek regulatory authorization and advance patent strategies in different jurisdictions. While no empirical basis is provided for this proposition, in practice regulatory and patent efforts made in the US are often mirrored or slightly delayed in Canada.

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[32] Patricia Laurens, et al., *Worldwide IP coverage of patented inventions in large pharma firms: to what extent do the internationalisation of R&D and firm strategy matter*, 80 INTERNATIONAL JOURNAL OF TECHNOLOGY MANAGEMENT, 6, 11 (2019).
[33] Id. at, 6, 20.

Finally, the measure of the impact of Canada's implementation of international obligations will be made on the basis of a quantitative comparative analysis of authorized biosimilars and their market availability, if launched, to determine whether and how the differences in the way Canada has implemented patent linkages, data exclusivity and additional IP provisions have impacted the market entry, or lack thereof, of biosimilars in comparison to the US and EU.

Given the highly coordinated global strategies in respect of patents and regulatory compliance, one may infer that differences observed are due to differences in domestic patent and regulatory regimes. While this may be an oversimplification, this research is of value as a starting point in the identification of the factors and their respective weights that affect the timing of biosimilar approval and launch in different jurisdictions.

1.3. Structure

This research is crafted to be a thorough analysis of the evolution of the international treaties, an examination of the differences in their implementation in Canada, the US and EU, and an investigation of whether any differences in the measurable results, namely the number biosimilars approved and launched, can be correlated to the differences in the way in which Canada has chosen to craft its national legislation arising from its international obligations in comparison to the American and European experience.

This work is divided into 6 chapters beginning with this introductory Chapter 1 providing the context of work, an overview of the international and national legal arenas that are to be examined and the legal methodology to be applied to this research.

Chapter 2 is an important foundation building section that is necessary to put the remaining material into appropriate context. Specifically, this chapter is an overview of the technology related to biologics and biosimilars which, as is subsequently addressed,

directly influences the way in which these therapeutic agents are both regulated and patented.

Chapter 3 is a thorough analysis of the evolution of international treaty obligations related to biologics and biosimilars and the way in which patent linkages, data exclusivity and additional IP protection provisions are approached in Canada, as well as the US and EU.

Following logically, Chapter 4 is an examination of the way in which Canada, in comparison to the US and EU, has chosen to meet, or not meet, their respective international treaty obligations. Finally, the chapter concludes with a quantitative assessment of biosimilars that have been approved and launched in each respective market. This data will be used as a measure of success in achieving the goal of facilitating the approval of safe and efficacious biosimilars while also incentivizing further innovation.

An analysis and discussion will then follow in Chapter 5 with a view to gleaning insight into the factors that influence the authorization of biologics and biosimilars based on each states' different approach to the implementation of their international treaty obligations.

There are a number of issues that will be touched upon during the course of this work that, while exceedingly interesting, is ancillary to the scope of this research. This work will not be an analysis or assessment of the laws, regulations or policies applicable to the commercialization, penetration into public and private payer markets (including considerations of formulary listing, substitutions and interchangeability), incentivization of R&D and public health policy as it relates to biologics.

Further, this work focuses on therapeutic biologics that have been generated through living organisms using recombinant technology. This excludes other biologically derived products regulated by Health Canada pursuant to Schedule D of the Canadian *Food and*

Drugs Act ("Canadian Food and Drugs Act")[34] such as blood and blood products, vaccines (even when produced by recombinant technology), radiopharmaceuticals and other biological products sourced primarily by fractioning or purification.[35]

1.4. Relevance

It is a goal of this work to provide an analysis of the impact that international obligations have had on Canadian patent and regulatory laws and policies and the resultant approvals and marketing of biosimilars in Canada. In addition to contributing to the discourse, this work represents an opportunity for an academic investigation into an area of private practice that I have been engaged with for almost two decades, the majority of the first decade of which was predominately pharmaceutical patent litigation, first brand and then generic, and life cycle management. I remain engaged in providing advice on the identification, acquisition, management and enforcement of intangible assets and intellectual property rights in many areas including in the biotechnology industry.

The biologics and biosimilars industry is rapidly becoming one of the most important and valuable global industries, but it is profoundly and prohibitively expensive.[36] Developing and facilitating the development and approval of biosimilars is viewed as a spur for competition which in turn will drive prices down[37] in an environment where both public and private payers struggle with the rising costs of biologics.[38]

Additionally, the analysis considers how Canadian patent and regulatory laws and policies may be adapted in the future to positively promote the development of safe,

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[34] Food and Drugs Act, R.S.C., 1985, c. F-27.
[35] For an overview of the differences in the biological products, please see Liu, ELECTROPHORESIS, (2000).
[36] Heidi Ledford, *First biosimilar drug set to enter US market*, NATURE, January 15, 2015. 2015. Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012). Tao Gu, et al., *Comparing Biologic Cost Per Treated Patient Across Indications Among Adult US Managed Care Patients: A Retrospective Cohort Study*, 3 DRUGS - REAL WORLD OUTCOMES (2016).
[37] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).
[38] Gu, et al., DRUGS - REAL WORLD OUTCOMES, (2016). Ledford, NATURE, 2015.

effective and fiscally responsible biologics and biosimilars – thereby facilitating the rapid adoption of more effective treatments in critically important and often chronic therapeutic areas – to the benefit of the public both in Canada and abroad. Further, insights arising from this research may provide direction into how Canada, as a nation and as a responsible international community stakeholder, can positively contribute at the international trade level to advocate for measures that work for Canada, not just the US, EU and the biopharmaceutical industry.

Exploration in this area will be invaluable in understanding how national policy goals – incentivizing biologics R&D, ensuring economical access to safe and effective biologics and biosimilars, and the furtherance of biotechnological knowledge for the betterment of Canadians – are influenced by international obligations and how national patent and regulatory frameworks may be crafted to achieve these goals in the years to come.

CHAPTER 2. Biologics – The Current and Future Importance of the Biologics and Biosimilars Industry

2.1. Introduction

The authorization and widespread adoption of biologics and biosimilars in Canada is of the utmost importance to the health and wellbeing of its citizens and has far-reaching economic impacts on the biopharmaceutical industry, public and private payer, in addition to patients. As will be addressed in the coming chapters, the way in which Canada has implemented its international obligations at a national level has had a profound effect on the regulation of this class of therapeutic drugs, the approvals of which are statutorily linked to patent and IP status. Prior to undertaking that analysis, however, an appropriate foundation of the biologics/biosimilars industry and technology, their regulation and the intellectual property considerations pertinent to biologics and biosimilars must be laid.

Sections 2.2 and 2.3 begins by answering the question "what exactly are biologics?" in order to put this important and valuable industry into context with Canada's international obligations and their impact on the regulation and patent protection of biologics and biosimilars. The technological realities warrant review and contextual consideration in order to better understand their implications through the progression of this work. Pharmaceuticals are chemically synthesized in a well-defined and controlled manufacturing process.[39] These manufacturing processes are generally well established and are accurately and predictably reproducible.[40] Consistency of the final pharmaceutical product is not often a challenge and is indeed the basis for the abbreviated pathway to approval based on the demonstration of bioequivalency. Biologics, on the other hand are large complex molecules produced by living organisms

[39] Leader, et al., NAT REV DRUG DISCOV, 21 (2008). Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. LEGIS. 363(2010).
[40] Liang, HARV. J. LEGIS., 371 (2010).

which are far more complex systems of manufacture.[41] One of the final stages of biologic production is the isolation and purification usually occurring in a series of steps any of which may actually be more complex than the entirety of a manufacturing process of a small-molecule pharmaceutical.[42] As one will see, these technological realities have an impact on the patenting and regulation of these therapeutics.

In terms of patents, Section 2.4 provide an overview of patent law fundamentals necessary to put the regulatory intersection with patent/IP clearance and remaining work into context; it establishes a foundation for the patent strategies employed by the biologics industry which is informed by the nature of biologics and biosimilars. From the perspective of national intellectual property regimes (harmonized through the international trade agenda over time), the underlying legal principles in each of their respective patent systems are quite similar in Canada, the US and EU. Also discussed in Section 2.4, three important legal changes directed by international treaty obligations have had specific impact on the pharmaceutical and biologics patent strategy, namely: (1) patent protection must be provided for pharmaceutical products, (2) the term of a patent must be 20 years from the date of filing and (3) the patent regime must be "first to file", not "first to invent". The complexity of biologics and biosimilars have generally given rise to more patents claiming "core" inventions (product, formulation and use of the product)[43] as well as "peripheral" patents claiming the underlying development, manufacturing, administration and treatment monitoring technology.[44] This reality gives rise to strategies for filing multiple, overlapping patents with potentially overbroad claims that serve to obfuscate the patent landscape for a particular biologic. These clusters of patents are sometimes referred to as "patent thickets".[45] As will become apparent in the coming chapters, a given biologic manufacturer's patent strategy has a material impact on the market authorization of biosimilars containing the same active

[41] Id. at, 370-1.
[42] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004).
[43] Jeffrey Wu & Claire Wan-Chiung Cheng, *Into the Woods: A Biologic Patent Thicket Analysis*, 19 CHI.-KENT J. INTELL. PROP. 93, 121 (2019).
[44] Id. at, 122.
[45] Id. at, 109-10.

therapeutic ingredient given its potential operative effect in the context of national patent linkage regimes, as well as additional patent-based or *sui generis* rights arising from eligible patents.

In Canada, as well as the US and EU, sophisticated and comprehensive laws and regulations have been established to evaluate and assess biologics and biosimilars both prior to approval and continued monitoring after launch.[46] The agencies responsible for the regulation of biologics and biosimilars are the same agencies responsible for the regulation of a variety of other therapeutic products, treatments and devices, including pharmaceuticals, namely Health Canada, the US' Food and Drug Administration (FDA), EU's European Medicines Agency (EMA). In respect of the regulation of biologics and biosimilars, groups within each of the previously named agencies have carriage of these evaluations, namely Health Canada's Biologics and Genetic Therapies Directorate (BGTD), the US FDA's Center for Drug Evaluation and Research (CDER) and the EMA's Committee for Medicinal Products for Human Use (CHMP) which provides central authorization for biologics and biosimilars for the European Economic Area.

While each jurisdiction has independent purview over the biologics/biosimilars that are granted market authorization, practically, there is significant international integration of standards and even reliance between these regulatory agencies. Thus, Canada's approach (as is the case in the US) to the regulation of biologics and biosimilars has been heavily informed by the EU's experience and focus on safety, efficacy and quality. In following the EU's lead, both the US and Canada have embraced a two pronged approach to establish the quality, safety and efficacy of a biosimilar; first, an assessment of biosimilarity based on the biosimilar's structure and function, and second, relying on non-clinical and clinical trials to establish that there is no clinically meaningful

[46] Montgomery, UNIVERSITY OF PITTSBURGH LAW REVIEW, (2015). Government of Canada, Guidance Document Information and Submission Requirements for Biosimilar Biologic Drugs (Health Canada ed., Health Canada - Publications 2017). European Medicines Agency, Guideline on Similar Biological Medicinal Products (Committee for Medicinal Products for Human Use (CHMP) ed., CHMP/437/04 ed. October 30, 2005). Leah Christi, FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US (CDER Food and Drug Administration ed.). Government of Canada, Biosimilar biologic drugs in Canada: Fact Sheet (Health Canada ed., 2019).

differences in terms of safety, quality and efficacy in comparison to the reference biologic.

In the case of the research at hand, there is no comparative analysis of the regulation of biologics and biosimilars in Canada vs. the US and EU. The important aspect of the regulatory foundation laid out in Section 2.5 in respect of these jurisdictions is not their differences, rather it is their commonalities that are of greater importance in this instance; it is critical to understand that the way that each of their respective regulatory processes are designed is to similarly interact with the patent/IP clearance regimes mandated by their international obligations and nationally implemented. Introduced in Section 2.5 and detailed in Chapter 4, after moving through similar regulatory assessments a biosimilar may still be market barred or subject to an administrative hold or stay due to (1) existing patents terms, the expiry or clearance of which is linked to regulatory approval (patent linkages), (2) data exclusivity prohibitions and/or (3) unexhausted *sui generis* rights, all of which are triggered at the same point in each jurisdictions' regulatory processes as a result of their commonalities. As will become apparent as this work progresses, patent and IP considerations may be an impediment not only to the market authorization grant, but also to the actual submission filing in Canada, as well as the US and EU. Thus, understanding the commonalities of the regulatory processes addressed in Section 2.4 is the critical foundation to understand the context of *when* in the regulatory process the patent linkages, data exclusivity and additional IP provisions – as mandated by international obligations as described in Chapter 3 – are triggered, the national implementation of which will be compared by jurisdiction in Chapter 4.

2.2. The Industry – An Economic Overview of Biologics and Biosimilars

The economic impact of biologics is of increasing global significance for a therapeutics industry that barely existed 30 years ago. It bears repeating that the global biologics market for 2019 has been pegged at USD$255B and estimated to grow to USD$457B by

2027.[47] Of greater importance than the money, however, is the human factor; the impact that biologics and biosimilars have on public health is astounding as patients suffering from diseases difficult to treat, or previously untreatable, now have a new source of hope. But, due to the complexities of biologics and their manufacture, the costs are extremely high,[48] potentially making the costs to patients and payers prohibitively high.[49] Strategies to increase the efficient adoption of biosimilars to promote competition and downward pressure on pricing needs to be cultivated.[50]

Over time, there has been a shift in the market share of the biopharmaceutical pie that pharmaceuticals are ceding to biologics. There has been a decline in the applications for market approval new pharmaceutical drugs since the mid-90s, but a comparable increase (lower in volume) in the applications for biologics and biosimilars in that same time period.[51]

Of the top 10 drugs by annual revenue in 2019, seven are biologics including the blockbuster arthritis/autoimmune biologic HUMIRA (adalimumab) and breast cancer biologic HERCEPTIN (trastuzumab).[52] Interestingly, in an American study in 2019, a survey of employers found that although biologics accounted for only 1% of all prescriptions dispensed to their workers and dependents, they accounted for 40% of all monies spent on drugs.[53]

The hope is that efficient adoption of competitive biosimilars will provide costs savings for patients and payers to not only halt, but reduce the costs of biologics. This strategy becomes particularly more pressing in light of the tendency for biologic companies to

[47] CMI. April 3, 2020. Research. 2020.
[48] Andrew W. Mulcahy, et al., *Biosimilar Cost Savings in the United States Initial Experience and Future Potential*, (2017). America, 1. 2018.
[49] Gu, et al., DRUGS - REAL WORLD OUTCOMES, (2016).
[50] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).
[51] Chris Morrison, *Fresh from the biotech pipeline-2019*, 38 NATURE BIOTECHNOLOGY (2020). Cormac Sheridan, *Fresh from the biologic pipeline-2009*, 28 see id. at (2010).
[52] Research. 2020. Stanton R. Mehr, *Where the US Biosimilars Market Is Heading and When It Might Get There*, (2020).
[53] Watson. August 20, 2019.

significantly increase their prices in the years leading up to the expiry of the biologic's patents and the entry of biosimilars on the market place. Two examples of this trend in the US market: Amgen increased the price for ENBREL (entanercept) by 37% over the course of 18 months from 2014 to 2016.[54] Janssen Biotech, the innovator biologic manufacture for REMICADE (infliximab), increased its prices by 57% from 2012 until the availability of the first biosimilar in 2017.[55]

The pharmaceutical industry has had a long history spanning over a century, tracing its roots back even further to the chemical industry. Indeed, many of the current pharmaceutical industry players today can trace their roots back to these chemical companies.[56] Like chemical companies giving rise to pharmaceutical companies, the majority in the biopharmaceutical industry are themselves pharmaceutical companies having expanded their therapeutic agent purview such as Pfizer and Merck. As well, traditional generic companies, such as Sandoz and Apotex, have moved into the biopharmaceutical space to not only produce biosimilars, but some have also advanced innovative biologic programs. Unlike these pharmaceutically-rooted companies, other ventures like Amgen and Genetech were founded as biotechnology companies that are now at the forefront of generating innovative biologics, but also engage in comprehensive biosimilars development strategies. The first category of pharmaceutical-grounded biologic/biosimilar manufacturers are more common; the major pharmaceutical players have been strategically making moves to shore up their biologics pipelines through development and acquisitions.[57] The second type of biotechnology-founded companies are less common, but have been driving the biologics

[54] Mehr, 30 (2020). ENBREL (entancercept), marketed by Amgen and Wyeth Pharmaceuticals, made an estimated $9.6 billion in global sales in 2019. See The Center for Biosimilars, *Etanercept Biosimilar Is Recommended for Use in European Union*, The Center for Biosimilars(March 27, 2020), *available at* https://www.centerforbiosimilars.com/news/etanercept-biosimilar-is-recommended-for-use-in-european-union-.

[55] Mehr, 30 (2020).

[56] DAVID C. MOWERY & RICHARD R. NELSON, SOURCES OF INDUSTRIAL LEADERSHIP : STUDIES OF SEVEN INDUSTRIES (Cambridge, UK
New York : Cambridge University Press. 1999).

[57] E. Moorkens, et al., *The Market of Biopharmaceutical Medicines: A Snapshot of a Diverse Industrial Landscape*, 8 FRONT PHARMACOL (2017).

innovation charge since the 1980s until the "big pharma" players began to engage more meaningfully in the pursuit of expanded pipelines and profits.[58]

The Interesting twist to the development of the biopharmaceutical activities is the blurring of lines between traditional "brand" or "innovative" companies with "generic" companies.[59] Of the top 25 biologics companies, about two thirds are traditional innovator pharmaceutical companies (such as Pfizer, Merck, Roche) where almost half of those innovator companies have biosimilar (such as Pfizer, Novartis, AstraZeneca) products and strategies. Similarly, of the two traditional generic pharmaceuticals on the list (Teva, Mylan), one is engaged in originator biologics development in addition to biosimilars development.[60]

Another interesting element is the geographic clustering of the top biopharmaceutical industry players which, as we will see in Chapter 3, has led to a concentration of geopolitical influence in the US and EU. Table 1 below sets out the top 28 pharmaceutical companies by global sales over the last decade (some of which have merged), detailing their founding origins, current headquarters and their current biologics/biosimilars offerings. Of the 28 top biopharmaceutical companies, 10 were founded in the US, 9 were founded in the EU, 9 founded outside of either the US or EU. In terms of headquarters, the concentration remains the US and EU where 14 companies are headquartered in the US and 8 are headquartered in the EU. Only 6 of 28 companies are located outside of the US or EU – 2 in Switzerland, 3 in Japan and 1 in Israel.

[58] Bruno Calo-Fernández & Juan Leonardo Martínez-Hurtado, *Biosimilars: company strategies to capture value from the biologics market*, 5 PHARMACEUTICALS (BASEL, SWITZERLAND) (2012);Moorkens, et al., FRONT PHARMACOL, (2017).
[59] Moorkens, et al., FRONT PHARMACOL, (2017).
[60] Id. at.

TABLE 1 – TOP 28 GLOBAL BIOPHARMACEUTICAL COMPANIES BY GROSS REVENUE 2010-2020

	Company	Traditional Market	Origin – Place, Founder nationality, Date	Current Headquarters	Biologics and/or Biosimilars
1	Pfizer	Brand Pharma	USA – Founded in 1849 in New York City, NY USA by German immigrants Charles Pfizer and Charles F. Erhart.	USA New York City, NY	Biologics Biosimilars
2	Novartis	Brand Pharma	Switzerland – Founded in 1996 from a merger of Ciba-Geigy (1971) and Sandoz Laboratories (1886).	Switzerland Basel, Switzerland	Biologics Biosimilars (Sandoz)
3	Hoffman-La Roche	Brand Pharma	Switzerland - Founded October 1896 by Fritz Hoffman-La Roche.	Switzerland Basel	Biologics
4	Merck US (MSD)	Brand Pharma	German – US Division opened 1891 NY, USA.	USA Kenilworth, NJ	Biologics Biosimilars
5	Sanofi	Brand Pharma	France – Founded in 1973 as result of merger between Elf Aquitaine and Labaz Group by French founders.	EU - France Paris, France	Biologics Biosimilars
6	Gilead Sciences	Brand Pharma	USA – Founded in 1987 under name Oligogen by American Michael L. Riordan in Foster City, CA USA	USA Foster City, CA, USA	Biologics
7	Johnson & Johnson	Brand Pharma	USA – Founded by Americans in January 1886 in New Brunswick, NJ	USA New Brunswick	Biologics
8	GlaxoSmithKline	Brand Pharma	New Zealand – Founded 1873 by Englishman Joseph Edward Nathan in Wellington, New Zealand.	EU Pre-2020 – UK Brentford, England, UK	Biologics
9	AstraZeneca	Brand Pharma	Sweden – Founded as Astra AB1913 in Södertälje, Sweden. Pharma division split and became British company Zeneca in 1993. Merged with Astra in 1999 and became AstraZeneca.	USA Cambridge, UK	Biologics Biosimilars
10	AbbVie	Brand Pharma	USA – Founded in 1888 originally as part of Abbott Laboratories by an American in Chicago. Abbott separated into 2 companies officially forming AbbVie in 2013.	USA Lake Bluff, Illinois, USA	Biologics
11	Amgen	Biotech	USA – First formed as Applied Molecular Genetics in 1980 by Americans in Thousand Oaks, CA	USA Thousand Oaks, CA USA	Biologics Biosimilars
12	Allergan	Brand Pharma	USA – Founded 1948 by American. Acquired by Irish-based Activis in 2015. Activis renamed Allergan plc and acquired by AbbVie in 2020.	USA Irvine CA Acquired by AbbVie in 2020.	Biologics Biosimilars
13	Teva	Generic Pharma	Isreal – Founded by American-Israelis May 1, 1935, in Jerusalem, Israel.	Isreal Petah Tivka, Israel	Biologics Biosimilars
14	Novo Nordisk	Brand Pharma	Denmark – Founded in 1989 by merger of Danish companies Nono Industri and Nordisk Gentofte in Bagsværd,	EU – Denmark Bagsværd, Copenhagen,	Biologics

	Company	Traditional Market	Origin – Place, Founder nationality, Date	Current Headquarters	Biologics and/or Biosimilars
			Copenhagen, Denmark.	Denmark.	
15	Eli Lilly	Brand Pharma	USA – Founded in 1876 by an American in Indianapolis, Indiana.	USA Indianapolis, Indiana, USA	Biologics Biosimilars
16	Bayer	Brand Pharma	Germany – Founded in 1863 by Austrians in Barmen, Wuppertal, Germany.	EU – Germany Leverkusen, Germany.	Biologics
17	Bristol-Myers Squibb	Brand Pharma	USA – Founded in 1989 by merger of Squibb and Bristol-Myers. Squibb founded by American in Brooklyn, NY, 1858. Bristol-Myers founded by American in Clinton, NY 1887.	USA 430 East 29th Street, New York City, NY, USA	Biologics
18	Takeda	Brand Pharma	Japan – Founded in 1781 by Japanese citizens in Doshomachi, Osaka, Japan.	Japan Tokyo, Japan.	Biologics
19	Boehringer Ingelheim	Brand Pharma	Germany – Founded in 1885 by Albert Boehringer in Ingelheim am Rhein.	EU – Germany Ingelheim, Germany	Biologics Biosimilars
20	Astellas Pharma	Brand Pharma	Japan – Founded in 2005 by merger between Yamanouchi (1923) and Fujisawa Pharmaceuticals (1894).	Japan Chuo City, Tokyo, Japan	Biologics
21	Mylan	Brand and Generic Pharma	Netherlands – Founded in 1961 by Danish founders.	USA Canonsburg, Pennsylvania, USA	Biosimilars
22	Biogen	Biotech	Switzerland – Founded in 1978 by US and German scientists.	USA Cambridge, Massachusetts, USA	Biologics Biosimilars
23	Celgene	Biotech	USA – Founded in 1986, after corporate spin-off from Celanese. Now owned by Bristol Myers Squibb	USA Summitt, New Jersey, USA	
24	Merck KGaA	Brand and Generic Pharma	Germany – Founded by Germans 1668, Darmstadt, Germany.	EU – Germany Darmstadt, Germany	Biologics Biosimilars
25	Daiichi Sankyo	Brand and Generic Pharma	Japan – Founded in 2005 by merger between Sankyo Company and Daiichi Pharmaceuticals, both pharmaceutical companies founded in Japan in the late 19th to early 20th centuries.	Japan Chuo City, Tokyo, Japan	Biologics Biosimilars
26	Baxter International Inc	Brand and Generic Pharma	USA – Founded in 1931 by Americans	USA Deerfield, Illinois, USA	Biosimilars
27	Sandoz	Generic Pharma	Switzerland – Founded in 1886. Novartis was created from the merger of Sandoz and Ciba-Geigy	EU – Germany Holzkirchen, Germany	Biosimilars
28	Shire Plc	Brand Pharma	UK - Founded in 1986 by UK entrepreneurs and acquired by Takeda in 2019	EU – UK Pre-2020	Biologics

The investment of both time and money necessary for the development of a biologic is staggering.[61] However, this issue – the calculation of innovation costs and input factors – has been highly controversial. For a more nuanced perspective, we must look to the body of research reporting widely different conclusions on this subject. In building on their own work over the last three decades, Joseph A. DiMasi, Henry G. Grabowski and Ronald W. Hansen provided updated research and development cost estimates of $2.8B.[62] Shortly after the publication of DiMasi's updated assessment, Vinay Prasad and Sham Mailankody reported their research criticizing the transparency and reproducibility of the DiMasi research and concluding that the mean cost to develop an oncology drug is approximately $648M.[63] The most recent statement on this issue was published in March 2020 by Oliver J. Wouters, Martin McKee, and Jeroen Luyten seeking to estimate the research and development costs required to bring a drug to market using publicly available data. Wouters reported a higher median cost of $780M and mean of $1.3B due to the way drug candidate failures were included in their methodology. As with Prasad, Wouters criticized DiMasi's use of confidential information voluntarily provided by companies without independent verification which is clearly problematic and a sounds basis to prefer Prasad and Wouters' findings over DiMasi's research despite its long range over time.[64]

To sum up tritely, the development of a biologic takes between 10-15 years and may cost upwards of USD $1 to 2 Billion.[65] Further, even if a drug does get to clinical trials,

[61] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).
[62] Joseph A. Dimasi, et al., *Innovation in the pharmaceutical industry: New estimates of R&D costs*, 47 JOURNAL OF HEALTH ECONOMICS, 31 (2016).
[63] Vinay Prasad & Sham Mailankody, *Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval*, 177 JAMA INTERNAL MEDICINE, 1573 (2017).
[64] Olivier J. Wouters, et al., *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018*, 323 JAMA, 851 (2020).
[65] Thomas Sullivan, *A Tough Road: Cost To Develop One New Drug Is $2.6 Billion; Approval Rate for Drugs Entering Clinical Development is Less Than 12%* (March 21, 2019), *available at* https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html.

the rate of eventual market approval is just over 10%.[66] On its face, the upfront investments necessary in R&D make clear the motivations of innovative biopharmaceutical companies which is to protect as much of their hard earned and commercialized work product as possible in order to be able to continue funding new drug development. Interestingly, there is a high direct correlation between the average spending on R&D over 10 years and the number of drugs approved.[67]

In terms of biosimilar development, the investments in generating a biosimilar is far from insignificant at an average of between USD$100-200 million and it can take 5-10 years before it gets to market. These are greater hurdles than those faced by generic pharmaceutical manufacturers. [68] However, the justifications underpinning the biosimilars industry are the same as for generics; biosimilars rely on previously developed technology to varying degrees to enter the marketplace and often tout the competition and price reductions as important public benefits of their efforts.[69]

But there is another side to this seemingly altruistic cycles of innovative biologic development and biosimilar accessibility considerations. Biopharmaceutical companies are going concerns that answer to shareholders and have tended to record profits that are statistically higher in comparison to non-pharmaceutical healthcare companies and non-healthcare companies on the S&P 500.[70] This is demonstrated by the rise in average after-tax profit margin of the top 25 drug companies (manufacturing biologics and

[66] See also Matthew Herper, *The Cost Of Developing Drugs Is Insane. That Paper That Says Otherwise Is Insanely Bad* (October 16, 2017), *available at* https://www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad/#6b90241e2d45. Mark Terry, *The Median Cost of Bringing a Drug to Market is $985 Million, According to New Study* (March 4, 2020), *available at* https://www.biospace.com/article/median-cost-of-bringing-a-new-drug-to-market-985-million/. Stanton R. Mehr, *Controversy Over the Cost to Bring Pharmaceuticals to Market*(September 13, 2017), *available at* https://biosimilarsrr.com/2017/09/13/controversy-over-the-cost-to-bring-pharmaceuticals-to-market/.

[67] Herper. October 16, 2017. Mehr, Controversy Over the Cost to Bring Pharmaceuticals to Market. September 13, 2017.

[68] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).

[69] Felix Shin, *Leaping from the Patent Cliff into the Global Drug Gap: Overcoming Exclusivity to Provide Affordable Biosimilars*, 37 LOYOLA OF LOS ANGELES INTERNATIONAL AND COMPARATIVE LAW REVIEW (2015).See also, Dawn Willow, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Health*, 6 CHICAGO-KENT JOURNAL OF INTELLECTUAL PROPERTY, 36-37 (2006).

[70] David M. Cutler, *Are Pharmaceutical Companies Earning Too Much?*, 323 JAMA (2020).

biosimilars, sometimes both) from 2010 to 2015 of 15% to 20%.[71] Further, Prasad found that the in 90% of the drugs investigated had higher revenues in comparison to development costs, the lowest of which was 17.5% up to a high of 6789.1% and 40% of the drugs investigated had revenues that exceeded development costs by at least 10-fold.[72] Regardless of the actual research and development costs – be it $648M,[73] $1.3B,[74] or $2.8B[75] - the risks associated with this investment will likely still not be outweighed by the profit potential, especially if strategies are available to prolong market exclusivity and, barring that, market dominance.

Much of the political scrutiny that the biopharmaceutical industry enjoys (or endures depending on perspective and issue) is a result of their economic, social, technological and legal influence on healthcare. Pharmaceutical companies routinely interacts with and influence governments around the world on matters having direct and indirect impacts on the regulation and protection of its products and their access to the markets.[76] To this end, the biopharmaceutical industry spends a ludicrous amount of money annually on lobbying efforts[77] in far disproportion to groups representing other health care stakeholders.[78]

For the purposes of the present research, the specifics and accuracy of DiMasi, Wouters and Prasad's works are of tangential relevance given that pricing of biologics and biosimilars are not substantially affected by legal and regulatory considerations. However, the actions and strategies of industry players influencing and leveraging legal

[71] Sharon Butt, *Big Money Club: Revealing the Players and Their Campaign to Stop Pharmacare*, 5 (March 2019).
[72] Prasad & Mailankody, JAMA INTERNAL MEDICINE, 1572 (2017).
[73] Id. at.
[74] Wouters, et al., JAMA, (2020).
[75] Dimasi, et al., JOURNAL OF HEALTH ECONOMICS, (2016).
[76] With corporate revenue streams greater than the GDP of some small nations, negotiations between large pharmaceutical companies and states can look more like a discussion among peers rather than an appeal to a governing authority.
[77] Susan Scutti, *Big Pharma spends record millions on lobbying amid pressure to lower drug prices at* https://www.cnn.com/2019/01/23/health/phrma-lobbying-costs-bn/index.html. Butt, 21 (March 2019).
[78] Robert Steinbrook, *Lobbying Expenditures, Campaign Contributions, and Health Care-Follow the Money*, 180 JAMA INTERNAL MEDICINE (2020).

and regulatory frameworks globally are ultimately dictated by their motivations including their risk-reward and bottom-line profit assessments.

2.3. The Technology – An Overview of Biologic/Biosimilar Biotechnology

Pharmaceuticals and biologics are like distant cousins with some similarities, but their similarities are not nearly as important as their differences. Understanding these inherent differences in the characteristics of biologics and biosimilars, as well as the complexities of their development, is imperative to understanding the impact these factors have on their regulation and patent strategies.

Pharmaceuticals are small molecule therapeutic agents with function determined through various biological assays for activities. They are generally not structurally complex, capable of being manufactured on an industrial scale, and are comparably thermo- and chemically stable.[79] Pharmaceutical investigation has generally taken the "shot-gun" approach.[80] That is, tens of thousands of possible therapeutic molecules are made then screened in a battery of diverse tests to determine whether there are any potentially therapeutic applications. Gradually, high potential candidates are selected to advance to further levels of screening and development into a commercially viable formulated product established to be safe and efficacious for a given indication.

Pharmaceuticals are then chemically synthesized in a well-defined and controlled manufacturing process.[81] These manufacturing processes are generally well establish and accurately and predictably reproducible.[82] Consistency of the final pharmaceutical product is not often a challenge and is indeed the basis for the abbreviated pathway to approval based on the demonstration of bioequivalency touched on in this chapter.

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[79] JOHN M. WALKER, et al., MOLECULAR BIOLOGY AND BIOTECHNOLOGY 307 (Cambridge : Royal Society of Chemistry 5th ed. / edited by John M. Walker, Ralph Raply [i.e. Rapley].. ed. 2009).
[80] Id. at.
[81] Leader, et al., NAT REV DRUG DISCOV, 21 (2008).
[82] Liang, HARV. J. LEGIS., 371 (2010).

Again, biologics and biosimilars are a different beast all together.[83] Biological molecules are, in comparison to small molecules, exponentially more massive in size and structurally complex including primary (amino acid sequence), secondary (basic protein folding), tertiary (complex protein folding) and quaternary (protein-protein interactions) features critical to the functioning of the resulting therapeutic. These significant complexities are the basis for the "biosimilarity" standard in respect of their regulation rather than an equivalence determination since there is no such thing as an "identical" or "generic" biologic.

Biologics and biosimilar can be loosely classified into three categories: monoclonal antibodies, enzyme replacement/modulators and replacement/modulators or cell-surface receptors.[84]

The early 80s saw the creation of the first generation of biologics were derived from human endogenous proteins (i.e., hormones and enzymes)[85] made using recombinant technology, namely combining genetic material from different organisms.[86] These biologics have evolved into an important and valuable class of biologics where the patents for the earliest of which have expired in the late 1990s, early 2000s.[87] As recombinant protein technology developed, the number of biologics under development comparably increased.[88] As a result of their designed specificity, one of the most important distinctions between biologics and the majority of pharmaceuticals is that their development has generally been targeted to specific biological molecules or

[83] For a better understanding of some of the ttechnical terms used in this work, there are a number of primers publicly available. See the US National Institute of Health's primer on DNA and genetics, "Help me Understand Genetics" at https://ghr.nlm.nih.gov/primer. Please see also, Guide to Biotechnology 2008. and for a more detailed primer, please see Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004).

[84] M. S. Kinch, *An overview of FDA-approved biologics medicines*, 20 DRUG DISCOV TODAY (2015). Leader, et al., NAT REV DRUG DISCOV, (2008).

[85] H. Schellekens, *When biotech proteins go off-patent*, 22 TRENDS IN BIOTECHNOLOGY, 406 (2004).

[86] Again, this biotechnology can get complicated quickly. For a great overview please also see Paul J. Carter, *Introduction to current and future protein therapeutics: A protein engineering perspective*, 317 EXPERIMENTAL CELL RESEARCH (2011).

[87] Schellekens, TRENDS IN BIOTECHNOLOGY, 406 (2004).

[88] Kinch, DRUG DISCOV TODAY, (2015).

pathways involved in particular disease states.[89] Indeed, the second generation of early biologics developed in the late 1990s were more complex macromolecules such as monoclonal antibodies. Initially, murine antibodies were not well tolerated, but the humanization and eventual development of recombinant antibodies resulted in the development of important biologics such as REMICADE (infliximab) and HERCEPTIN (trastuzumab).[90] As discussed in this research, the patents related to these biologics have had far-reaching effects on biosimilar development beyond just the scope of the claims and terms of the patents, many of which are recently expired or close to expiry.

These technological realities and their implications bears some review and contextual consideration: understanding the technological incongruity of biologics/biosimilars versus brand/generic pharmaceuticals is essential to contextualizing the differences in the regulation and patenting strategies. This is not an apples to oranges assessment; it is more like apples to pygmy hippopotami.

The technology that goes into the research, identification, purification/manufacturing and development of a biologic is significantly more complex in comparison to pharmaceutical development and manufacture. Broadly speaking, biologics are derived from biotechnology tools which are biologically sourced or use biological systems in their manufacturing.

More particularly, biologics involve the use of cells/cell-lines, vectors, plasmids, DNA/RNA PCR technology, and the use of biological or microbiological systems and genetic engineering – such as plant and animal cells, viruses and yeasts – to commercially produce therapeutic products. In comparison to pharmaceutical

[89] B. K. Chen, et al., *Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court's Recent Rulings do not Solve Fundamental Barriers to Competition*, 78 DRUGS (2018).
[90] Sirid-Aimée Kellermann & Larry L. Green, *Antibody discovery: the use of transgenic mice to generate human monoclonal antibodies for therapeutics*, 13 CURRENT OPINION IN BIOTECHNOLOGY (2002).

development, the complexities involved in the path to a biologic product are vast which leads to more intricate patent and regulatory issues and strategies.[91]

Inherent variation arises from the fact that the biological systems used to produce the biologic is less controllable than a chemical process. There is variability from batch-to-batch (biologic or biosimilar) even within a given process used to produce biologics according to a specific protocol. This kind of cellular or organically-based synthesis is simply not nearly as reproducible with the same accuracy or consistency as is the chemical processes that yield pharmaceutical products.

Variations will also arise that are inherent in the biologic processes that produce the biologics. For instance, in the production of proteins does not only involve the relatively consistent reproduction of a specific polypeptide sequence from a designed nucleotide sequence. Variations go beyond just the sequence of the protein and include the posttranslational modifications that will dictate many of the important characteristics of the end-biological products. These characteristics will be affected to varying degrees by slight differences in the raw materials or the biological platform from which these biologics are manufactured. For instance, posttranslational modification of polypeptides can include the addition of sugars (i.e., glycosylation) lipids or other functional groups including the addition of phosphate or acetate. The structural characteristics are as equally important to the activity of the biologics product including the formation of the secondary and tertiary structures that involve further chemical modifications (i.e., disulfide bridges or hydrogen bonding). Finally the interaction with other peptides in order to form protein complexes are important quaternary structural characteristics that affect the biological activity of the end product.[92]

[91] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004). Johnson, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2008).
[92] Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004).

The important difference in the characteristics between pharmaceuticals and biologics, and their impact at different stages from development to manufacture, is summarized below in the following table:

TABLE 2 – COMPARISON OF THE CHARACTERISTICS OF BIOLOGICS AND PHARMACEUTICALS[93]

Stage	Biologics	Pharmaceuticals
Physio-Chemical Structure	Large and biologically and chemically complex	Small and chemically less complex
Product Characterization	Difficult to fully characterize due to complexity and the variability of the resultant mixture of heterogeneous products	Homogenous final product chemically well characterized
Manufacturing Complexity	Highly complex manufacturing in living systems	Relatively simple manufacturing process primarily through chemical synthesis
Isolation and Purification	Lengthy, multi-stage purification process; Low tolerance of variability; detection of contaminant is difficult and almost entirely unable to be removed.	Generally easy to purify; Contamination more easily avoided, detected and removable.
Analysis	Potentially complex physiochemical analytical methods or biological assays	Analysis relatively simple laboratory analysis
Environmental Susceptibility	Highly susceptible to environmental variations in temperature, humidity	Environmental changes have very little impact.
Immunogenicity[94]	Likely has immunogenic effects impacted by post-translational modifications and process variations.	Generally low immunogenicity

What does all of this mean? First, it means that minor differences in manufacturing processes can lead to variations in the biologic that can significantly modify the

[93] Differences in characteristics have been aggregated and compiled from a variety of sources. See Liang, HARV. J. LEGIS., (2010). Leader, et al., NAT REV DRUG DISCOV, (2008);Kleinberg & Mosdell, AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (2004). Ohly & Patel, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, (2011). Carter, EXPERIMENTAL CELL RESEARCH, (2011).

[94] Immunogenicity means the ability of an agent to produce an immune response in the body. This is a very significant issue that can be profoundly unpredictable and potentially life-threatening. See the European EPREX immunogenicity issue described in the following articles for further context: Kanter & Feldman, HASTINGS LAW JOURNAL, 66 (2012). Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. U. L. REV. 883, 892 (2016).

molecule stability, activity, specificity, or antigenic properties in comparison to the reference biologic. Second, the regulatory assessment of a biosimilar is inherently and profoundly different than the bioequivalency comparisons drawn between brand and generic pharmaceuticals. Third, the inherent biologic variability may significantly affect the treatment of a patient may lead to either an adverse immune reaction to the biosimilar in comparison to the reference biologic, or a stronger or weaker than expected effect on the intended target, or even interactions with unintended targets. Fourth, the less consistent reproducibility, accuracy, and predictability inherent in biologic manufacturing processes result in risks that dictate a higher standard for the assessment of biosimilarity of the biosimilar in comparison to the reference biologic. And ultimately, it means that the development of biosimilars takes more time, costs more money and is more complex than the development of generic pharmaceuticals.

Consequently, biosimilars must be regulated differently, they must be approved differently, and they must be incentivized differently.

2.4. The Patents

Technological differences described in this chapter have a significant bearing on the patent strategies employed by biologic and biosimilar companies. However, it is the intersection of these patent strategies with the regulatory frameworks that, as will be described further in this chapter, is of particular interest to this research. A general foundation of patent law principles, predominantly agnostic to the field of technology, is first warranted.

In Canada, the US and EU, an invention is patentable where it is new, useful, not obvious and of patentable subject matter.[95] As described in more detail in Chapter 3, the harmonization of many fundamental aspects of patent law applicable to biologics and biosimilars arose from international treaty obligations and are now entrenched in

[95] Canadian Patent Act s. 2, 28.2, 28.3. US patentability criteria: 35 USC §101, 35 USC § 102, 35 USC § 103, 35 USC § 112. European Patent Convention (2000) at Article 52(1).

Canada, the US and EU. In particular, patent protection must be provided for patentable subject matter in all fields of technology including pharmaceutical products,[96] the patent term must run for 20 years from the date of filing,[97] and the patent system must be based on "first to file", not "first to invent", a change that had specific impact in the US in 2010 discussed below.[98]

In terms of crafting the specific protections, patent claims define the fence around the invention where the patentee is able to exclude others from treading upon. The way that the claims of a patent defines this fence influence the ways in which a pharmaceutical and biologic company can enforce these exclusionary rights. For example, the technology involved in manufacturing a new drug or biologic can be embodied in a number of different types of claims which commonly include, but are by no means limited to, the following: medicinal ingredient,[99] products,[100] formulation,[101] dosage form,[102] product by process,[103] process,[104] and use of the product.[105] These protections are designed to be layered, their protection compounding; if a company obtained only a process patent, but not a product patent, another company could manufacture the product by a non-patented process, thereby not infringing the

[96] Agreement On Trade-Related Aspects Of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) Article 27.1.
[97] Id. at, Article 33.
[98] Candice Decaire, et al., *Negotiating a new legal landscape: the advent of follow-on biologics*, 46 UNIVERSITY OF SAN FRANCISCO LAW REVIEW (2012).
[99] A claim in the patent for the medicinal ingredient, whether chemical or biological in nature, when prepared or produced by the methods or processes of manufacture particularly described and claimed in the patent, or by their obvious chemical equivalents, and also includes a claim for different polymorphs of the medicinal ingredient, but does not include different chemical forms of the medicinal ingredient.
[100] Product claims could relate to the medicinal ingredient, formulation, dosage form.
[101] A claim for a substance that is a mixture of medicinal and non-medicinal ingredients in a drug and that is administered to a patient in a particular dosage form.
[102] A claim for a delivery system for administering a medicinal ingredient in a drug or a formulation of a drug that includes within its scope that medicinal ingredient or formulation.
[103] A claim for a product – medicinal ingredient, formulation, dosage form – made by a particular process.
[104] A claim for a process of manufacture of a therapeutic product, formulation and/or dosage form.
[105] A claim for the use of the medicinal ingredient for the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms.

patentee's process patent.[106] However, given the relative newness of biotechnology, there is a greater amount of potentially patentable technology that goes into a biologic, the development of a biologic and *potentially* the development of biosimilars including inventions that cover cell lines, animal models, vectors, genetic materials, gene sequences, protein sequences, etc. This includes patent strategies to protect important aspects of their technology inherent in the active/medicinal ingredient, formulation, production process, and use of the biologic/biosimilar.[107] As we will see throughout this work, these perceived entitlements have the potential to lead to entanglements resulting in a lack of biosimilar incentivization.

As previously discussed, the pharmaceutical industry has had a long history spanning over a century and stemming from the chemical industry. Indeed, many of the current major biologic industry players are these same pharmaceutical companies that can trace their roots back to these chemical companies.[108] Many of these companies are well versed in the importance of intellectual property protection so it should come as no surprise that biologics and even biosimilar companies seek to protect their innovation by a variety of means including patents. Indeed, the protection of intellectual capital has been the driving force behind many strategic plans of biologic companies, including R&D, co-development agreements, assignment and licensing of technology, mergers & acquisitions of other companies, etc. and other strategies to consolidate and capture their intellectual property.[109]

Proponents of an aggressive patenting strategy argue that broad patent protection is warranted to protect market exclusivity and resulting profits in order to fund the R&D cycle which is extremely time consuming, inherently risky, and wildly expensive.

[106] This is what was statutorily allowed to happen in India in the 1970's when the government (heavily influenced by the strong domestic generic pharmaceutical manufacturing industry) mandated that pharmaceutical products were not patentable per se, but processes of their manufacture were.
[107] Moorkens, et al., FRONT PHARMACOL, 9 (2017). Wu & Cheng, CHI.-KENT J. INTELL. PROP., 121-122 (2019).
[108] See Section 2.1, MOWERY & NELSON. 1999. Chapter 7, The Pharmaceutical Industry and the Revolution in Molecular Biology: Interactions Among Scientific, Institutional, and Organizational Change, Rebecca Henderson, Luigi Orsenigo, Gary P. Pisano 269-275
[109] Moorkens, et al., FRONT PHARMACOL, 10 (2017).

However, the counter-perspective is that overly broad patent protection, namely a less stringent assessment of the patentability of a given invention before the patent office, will significantly deters innovation by anyone other than the brand first to the finish line.

Patent rights, like many other intellectual property rights, are exclusionary in nature, but do not necessarily confer the exclusive ability to commercialize a product that may (directly or indirectly) fall within the scope of a patent(s). Rather, a patent confers the right to exclude others from practicing the claimed invention. Accordingly, acquiring patent rights for a maximum number of possible claim types is the first line of defense that a biologics company has to protect its valuable intellectual capital from potential biosimilar competition. This propensity contributes to the creation of clusters of patents related not only to the biologic, but also technology overlapping with the biologic creating "patent thickets" that are difficult to identify and navigate.[110] In recent years, even the EPO has identified the shift in patent strategy that is attributable to macromolecular patent filings which has seen a significant increase.[111] It has been proposed that the shift from a "first to invent" to a "first to file" system is the impetus for patent filings that are so early in the development of the biologic that the claims will tend to be speculative, overbroad and plentiful.[112] However, the converse is also true; patents can be filed at any time during the development of the biologic and well after launch which may only be tangentially related to the biologic. The presumed underlying intention is to create barriers to biosimilar competition. For instance, it was reported that the majority of over a hundred patents related to HUMIRA (adalimumab) was filed

[110] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019).
[111] Dietmar Harhoff, et al., *The strategic use of patents and its implications for enterprise and competition policies*, (2007).
[112] Decaire, et al., UNIVERSITY OF SAN FRANCISCO LAW REVIEW, (2012). Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019).

in 2010 well after its market launch which, once challenged by biosimilar manufacturers seeking approval, asserted infringement of 74 patents.[113]

Where patent thickets serve to build fences around the inventive elements of the biologic, all fences must eventually come down as patents expire. Expiry of a patents that may be asserted against a biosimilar is referred to as "patent cliffs" that represents the end the primary scope of patent protection that usually claim products, manufacturing processes, formulations, use, etc. A significant amount of effort and analysis is undertaken to determine when the timing of these patent cliffs which greatly informs a biosimilar manufacturer's strategy in targeting specific biologics with which to compete. The Generics and Biosimilars Initiative Journal published a broadly encompassing review of estimated patent cliffs for monoclonal antibodies (non-humanized and humanized) and non-antibody biologics taking into consideration both patent expiry and data exclusivity assessments.[114] Further, Hubb Schellekens' work in the area reports the expiry of the first wave of biologics developed in the 1980s, namely hormones and enzymes, which have expired during the early 2000s.[115] For the second wave of biologics developed in the 1990s, the patent cliff for many of these biologics (e.g. RITUXAN (rituximab), REMICADE (infliximab), AVASTIN (bevacizumab), HERCEPTIN (trastuzumab), ENBREL (etanercept) has been occurring over the last few years to date.[116] However, there has been an obscuring of these patent cliffs by the patent thickets due to a blurring of claims that may be asserted against a biosimilar applicant in the course of its regulatory approval process by a reference biologic holder. These data should be approached with some caution given that the patent thickets applicable to a given biologic may be dense and no underlying patent information is provided in order to verify the scope of the patent searches that underlie the reported results. Without

[113] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019). Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions* The New York Times(July 15, 2016), *available at* https://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html.

[114] B. I. Journal Editor Ga, *Patent expiry dates for biologicals: 2018 update*, 8 GENERICS AND BIOSIMILARS INITIATIVE JOURNAL 24(2019).

[115] Schellekens, TRENDS IN BIOTECHNOLOGY, (2004).

[116] Calo-Fernández & Martínez-Hurtado, PHARMACEUTICALS (BASEL, SWITZERLAND), (2012).

doubt, however, these assessments provide some insight into the approximate protection periods, a necessary starting point in determining whether the de facto period of protection has been inappropriately extended and why.

Thus, patent thickets are not only daunting and a significant barrier to biosimilar competition,[117] they also serve to obscure the patent cliffs, deter expensive patent litigation and encourage private settlement of patent litigation and licensing agreements that may artificially extend the biologic monopoly and establish a royalty stream once biosimilar competition does come on the market. This is currently the state of affairs in the case of HUMIRA (•), the single highest grossing drug in the world at $20B annually and growing, where AbbVie will enjoy a market exclusivity period for a total of three decades, well beyond the 2012 expiry of the product patent. These far-reaching implications will be addressed in more detail in Chapter 5's analysis and discussion.

As previously alluded to, patent strategies take a more prominent position in the biopharmaceutical industry. In countries where patent linkages are enshrined in national legislation, the reference biologic holder's patent(s) are linked to the regulatory approval of competing biosimilars which is why these regimes are referred to as "patent linkage" regimes. Introduced in the following section, the underpinnings for patent linkages at the international treaty level is explored in Chapter 3, their comparative national implementations examined in Chapter 4 and their implications discussed in Chapter 5.

Importantly, there exists in Canada, the US and EU, exceptions that allow a biosimilar applicant to practice the invention for experimental or regulatory purposes; activities that would otherwise be infringing. These types of provisions can be referred to as early-working or regulatory use exceptions/exemptions.

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[117] Cynthia Koons, *This Shield of Patents Protects the World's Best-Selling Drug* Bloomberg Businessweek(September 7, 2017), *available at* https://www.bloomberg.com/news/articles/2017-09-07/this-shield-of-patents-protects-the-world-s-best-selling-drug.

In Canada, the s.55.2 early working exception enacted in the Canadian Patent Act[118] applies to an otherwise infringing activity where the activity is done solely for uses reasonably related to the development and submission of regulatory information.[119] These regulatory requirements can be pursuant to federal or provincial law, or the laws of another country. While this provision is not specifically addressed to the pharmaceutical industry, it has been used almost exclusively by generics and more recently biosimilar manufacturers as an early-working exception for the purpose of preparing submissions to Health Canada to obtain market authorization.

The Canadian PM(NOC) Regulations were enacted pursuant to s.55.2(4) of the *Patent Act* with the intent of balancing the generic's early working activities under s.55.2's Regulatory Use Exemption against the Brand's intellectual property rights.[120] The Canadian government's intent to balance these competing interests was clearly reflected in the Regulatory Impact Analysis Statement of the Canadian PM(NOC) Regulations as originally enacted in 1993 which states:

> These Regulations are needed to ensure this new exception to patent infringement is not abused by generic drug applicants seeking to sell their product in Canada during the term of their competitor's patent while nonetheless allowing generic competitors to undertake the regulatory approval work necessary to ensure they are in a position to market their products immediately after the expiry of any relevant patents.
>
> …
>
> These Regulations together with subsection 55.2(1) will allow patentee to enjoy full patent protection while ensuring off-patented competitors will be able to enter the marketplace immediately upon the expiry of all patents pertaining to a medicine.

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[118] *Patent Act* at s. 55.2(1). The s.55.2 Regulatory Use Exemption applies to otherwise infringing acts where they are solely and reasonably related to the development and submission of regulatory information. While this provision is not specifically addressed to the pharmaceutical industry, it has been used almost exclusively by generics as an early-working exception for the purpose of preparing submissions to Health Canada to obtain market authorization.

[119] If a patented process is used solely to make material required for regulatory purposes, that act is exempt. If the process has an ancillary purpose, such as stockpiling material for later commercial sale, it will not be exempt even if some material is used for regulatory purposes.

[120] Canada's s.55.2 Regulatory Use Exemption was challenged by the European Union before the World Trade Organization in 1998 where Canada successfully argued that this exception qualified as limited exception under Article 30 of the TRIPs Agreement.

However, it is important to note the historical context that eventually lead to the enactment of Canada's s. 55.2 early working exception and the Canadian PM(NOC) Regulations in 1993, namely the abolition of the compulsory licensing regime that allowed Canada's generic pharmaceutical industry to flourish.

Dating back to 1923, Canada's patent laws provided for the issuance of compulsory licenses for the manufacturing and importation of patented medicines.[121] A compulsory license was a statutory license, the patentee's consent to which was not required, allowing a generic manufacturer to make and sell a generic version of a brand pharmaceutical that was still under patent protection where the pharmaceutical's active ingredient was manufactured in Canada. In exchange, the patentee received a fixed royalty to be paid by the generic which were set at 4% of the retail drug price.[122] In 1969, an amendment to the Canadian Patent Act allowed compulsory licenses to cover instances where the active pharmaceutical ingredient was manufactured outside of Canada, thereby allowing for the importation of the active pharmaceutical ingredient, then subsequent compounding in Canada. This lead to an exceptionally strong generic manufacturing industry which clearly caught the attention, and garnered the pressure, of the brand pharmaceutical industries in the US and EU, eventually being identified as incompatible with its international obligations. Unfortunately, the pendulum likely swung too far; Canada was experiencing a negative effect of reduced innovation, investment and loss of highly educated Canadians to other jurisdictions that eventually spurred the federal Minister of Consumer and Corporate Affairs in the mid-80s to strike a commission to investigate a rebalancing of Canada's compulsory licensing regime in order to generate growth and strengthen Canada's innovative industry. Thus, this represented a tectonic shift in the Canadian legal landscape relating to pharmaceutical patent law that, as we will see in this chapter and Chapter 4, ultimately lead to the current pendulum swing in the other direction.

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[121] Margaret Smith, Patent Protection for Pharmaceutical Products in Canada - Chronology of Significant Events § PRB 99-46E (Law and Government Division ed., March 30, 2000).
[122] *Bristol-Myers Squibb Co. v. Canada (Attorney General)* (2005), 2005 SCC 26 at paras. 8—10.

In the US, the regulatory use exception arose from Congress' response to a decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.* ("Bolar Exception").[123] In *Eli Lilly and Co. v. Medtronic, Inc.*, the US Supreme Court grant the patent term extension pursuant to §156(f) to Eli Lilly, however, the Court also interpreted Congress' actions in adopting the Bolar Exception codified in §271(e)(1), applying to all human drugs, whether chemical or biological, stating that "[i]t shall not be an act of infringement to make, use, or sell a patented invention … solely for uses reasonably related to the development and submission of information under Federal law which regulates the manufacture, use, or sale of drugs."[124]

An early working exception has also be adopted in the EU, but not until after it unsuccessfully challenged Canada's early working exception. Discussed in detail in Chapter 3, the TRIPs agreement allows, among other things, states to use the WTO's enforcement mechanism for disputes that may arise. The EU brought a complaint against Canada taking issue with Canada's early working exception that also provided some stockpiling rights to generic manufacturers. Article 7 of TRIPs allows for significant flexibility whereby WTO states are enabled to implement their TRIPs obligations as well as give consideration to their other public policy objectives.[125] This issue was put to the WTO Panel by the EU arguing that the reference to measures consistent with TRIPs Article 8(1) meant that any other considerations beyond the patent holders rights were subordinate to the protection of the minimum intellectual property rights guaranteed by TRIPs.[126] That is, the early working exception, as well as the stockpiling provisions, were contrary to Canada's TRIPs obligations. Instead, the Panel accepted that Canada's adjustments to a patent holder's rights in the form of the early working exception were contemplated according to the objectives and principles (and other relevant provisions)

[123] *Roche Products, Inc. v. Bolar Pharmaceutical Co*, 733 F.2d 858 (1984), 221 USPQ 937 (Fed. Cir. 1984)
[124] *Eli Lilly and Co. v. Medtronic, Inc.*, 496 US 661 (1990) at 671-679. See also M. D. Kretzschmar, *Drug safe harbour provisions in the USA and Europe: implications for the emerging biosimilars industry*, 9 JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE 298(2014).
[125] See for example, IP/C/W/296, 3 and 6
[126] WT/DS114/R, 50.

of TRIPs.[127] The stockpiling provisions, however, were held to be problematic and were eventually eliminated. Subsequently, the EU adopted that states that "[c]onducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."[128]

The agencies responsible for the adjudication of patents warrant mention. The intellectual property offices in Canada and the US are responsible for the examination of patents, respectively the Canadian Intellectual Property Office (CIPO) and the United States Patent and Trademark Office (USPTO). Patent prosecution in the EU is a bit more complicated; the European Patent Convention was created to provide a coordinated, more efficient, less expensive pathway to patent grant in multiple countries. Beginning with 16 signatories in the 70s, the EPC is administered by the European Patent Organization which has grown to a total of 38 members including all 28 members of the EU plus other countries like Norway, Switzerland and Turkey.[129] Like the PCT, an applicant can file a single patent application that, if granted, is a valid and enforceable unitary patent in all of the member states that the applicant elects. Importantly, the European Patent Office administering the European Patent Convention is not a body of the European Union; patents are granted by the EPC for each country, but must be enforced in each jurisdiction.

[127] WT/DS114/R, 154
[128] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (November 20, 2001).
[129] *The EPO at a glance*, *available at* https://www.epo.org/about-us/at-a-glance.html.

2.5. The Regulations and Linkages – Biosimilar Regulatory Approvals and their Intersection with Internationally Mandated, Nationally Implemented Patent Linkages, Data Exclusivity and Additional IP Provisions

The importance of the early working exceptions crafted into the national patent laws in Canada, as well as the US and EU, goes beyond a simple exception to patent infringement and their associated legal consequences. These provisions provide biosimilar manufacturers a "jump" on the regulatory process in order to secure authorizations simultaneous with engaging in patent/IP clearance activities such as patent litigation, if warranted. Further, this "jump" is not only with respect to "infringement" time, namely the ability to practice protected invention(s) prior to the patent expiry – but also in respect of "regulatory" time where the ability to file an application for market authorization is also provided prior to the patent(s) expiry and/or potentially where data is also protected from certain types of use pursuant to data exclusivity protections as described below and detailed in Chapters 3 and 4.

In Canada, the US and EU, the standards for both the biologic and biosimilars are identical, namely safety, efficacy and quality.[130] A biologic applicant will be granted market authorization if its submitted evidence in respect of the biologic supports these criteria. The main distinction between the regulatory approaches for a biologic versus a biosimilar is the pathway. The biologic pathway is based on the submission of complete evidence and data establishing the safety, efficacy and quality of the biologic. However, there is an abbreviated pathway available to biosimilars relying on evidence and data already submitted by the previously approved biologic applicant. In Canada, and the US and EU, an abbreviated pathway for the assessment of biosimilars has been created such that their biosimilar application may compare or make reference to a previously

[130] Suraj Mulaje, *Procedure For Drug Approval In Different Countries : A Review*, 3 JOURNAL OF DRUG DELIVERY AND THERAPEUTICS (2013).

approved biologic often called a “reference product”, “reference medicine”, or “reference biologic product” (referred throughout as a reference biologic).

This section first addresses the technological realities of biologics and biosimilars that have shaped the principles underpinning the regulatory regimes in Canada, the US and EU, all of which are highly similar. With this context of how technology impacts biosimilar regulation, we next explore the specifics of abbreviated approval pathways for biosimilars using the EU as the starting point which accurately reflects reality; the EU pioneered the abbreviated biosimilar assessment framework which heavily influenced both Canada and the US’ efforts years later. Finally, we tie together the regulatory framework by describing the intersection between biosimilar regulation and the internationally mandated, nationally implemented patent linkages, data exclusivity and additional IP provisions, the comparative analysis of which will be addressed in detail in Chapter 4.

2.5.1. How Biosimilars Technology Shaped Their Regulation and Approval

The very nature of biologics and the technology behind their manufacture means that it is impossible to create an identical copy, or even close facsimile, of the active ingredient which is by and large possible in the brand/generic pharmaceutical paradigm. These technological realities alone impacts the development of biologics and biosimilars as well as their regulatory assessments.

Biologics and biosimilars are approved by a regulatory agency that, having received and reviewed detailed data and evidence submitted, support the safety, efficacy and quality of the biologic or biosimilar; these standards are equally applicable to biologics and biosimilars in Canada, the US and EU as detailed below. The key to the abbreviated biosimilars pathway is through establishing “biosimilarity” with a reference biologic.

Demonstrating that a biosimilar is “biosimilar” to a reference biologic is complex; the reference biologic holder has extensive knowledge and information about the

development and manufacturing of the reference biologic including established controls and specification tolerances.[131] By contrast, the biosimilar manufacturer has independently developed a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, controls, and specification tolerances) from the reference biologic manufacturer. It is not an insignificant proposition to conduct the necessary analysis to establish structural and functional similarity.[132]

Evidence for biosimilarity is founded upon structural and functional studies which, in the past have been very difficult to establish due to the state of the relevant technology. The good news is that advancements in analytical methodologies has increased the ability to extensively characterize the structural and biological properties, as well as increased the ability to identify and characterize the excipients and product- and process-related impurities. However, while these advancements allow a manufacturer to ascertain some differences, this has not translated to the capability to detect all relevant structural and functional variations between a biologic and biosimilar.

Focusing on biosimilars, three significant ways that inject variability between a biosimilar and a reference biologic are (1) the primary sequence of amino acids; (2) post-translation modifications such as glycosylation (addition of sugar moieties) or other side chains such as phosphorylation; and (3) tertiary (protein folding) and quaternary (protein-protein interactions) structure.[133] The latter two factors are especially susceptible to minor variations in formulation and environmental conditions, including light, temperature, moisture, packaging materials, container closure systems, and delivery device materials.[134] Each of these factors (in addition to others) may lead to a

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[131] Edward L. Korwek, *What Are Biologics - A Comparative Legislative, Regulatory and Scientific Analysis*, 62 FOOD & DRUG L.J. 257(2007).

[132] United States of America, Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (CDER Food and Drug Administration ed., May 2019).

[133] Devesh Radhakrishnan, et al., *Strategies to enhance productivity and modify product quality in therapeutic proteins*, 22 CURRENT OPINION IN CHEMICAL ENGINEERING 81(2018).

[134] America, Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations. May 2019.

lack of homogeneity in the resulting product when compared to the reference biologic, even in the event of strict control. Indeed, even mild variations in the production conditions of the reference biologic may lead to heterogeneity from batch to batch in both the biologic and biosimilar manufacturers' process.[135] Further, these inherent variabilities arising from the process and product purity may have unintended and unpredicted immune responses.

Additionally, different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. For example, differences in biological systems used to manufacture a protein product may cause different posttranslational modifications, which in turn may affect the safety and/or effectiveness of the product. Thus, when the manufacturing process for a marketed protein product is changed, the application holder must assess the effects of the change and demonstrate—through appropriate analytical testing, functional assays, and/or in some cases animal and/or clinical studies—that the change does not have an adverse effect on the identity, strength, quality, purity, or potency of the product as they relate to the safety or effectiveness of the product.

Finally, the biosimilar's mechanism of action leading to a clinical effect may not be entirely congruent with the reference biologic; further animal studies and human clinical studies will likely continue to be required in order to demonstrate biosimilarity.

It should be noted that this abbreviated pathway does include significantly more comprehensive data to establish biosimilarity than is required to establish bioequivalence in the generic pharmaceutical context. Not only does the biologics and biosimilars manufacturers have to overcome the vast amount of time, money and resources required to develop a biologic/biosimilar, but it must also contend with a comparably more difficult regulatory assessment and ongoing regulatory submission requirements internationally in comparison to pharmaceuticals.

[135] Radhakrishnan, et al., CURRENT OPINION IN CHEMICAL ENGINEERING, (2018).

2.5.2. Regulation of Biosimilars in Canada, the US and EU

Without question, the EU's European Medicines Agency has been at the forefront of the regulation of biologics and biosimilars. Both the Canadian and the US' approaches were influenced heavily from the EU's prior experience. As a result, the EU's approach will serve to set the stage to be followed by a description of the highly similar strategies employed in Canada and the US. [136]

The practical implications arising from the inherent variability of biologics and their manufacture (not present in the pharmaceutical context) means that the regulatory approach to biologics and biosimilars has had to evolve. Recognizing these fundamental realities, a high level approach was first adopted in the EU and then subsequently in the US and Canada, namely the assessment of a biosimilar is based on whether it is similar ("biosimilar") to the reference biologic or at a higher standard, interchangeable with the reference biologic.

The EMA is responsible for the assessment of applications made through a centralized marketing authorization process in respect of new medicines, including biologics and biosimilars, in the EU. While the EU's pharmaceutical regulation also has a decentralized and national procedure for obtaining marketing approval in EU member states, the unified procedure through the EMA is compulsory for biologics and biosimilars, in addition to other medicines.[137]

[136] Unlike the US and Canada, the EMA has set out product-specific guidance that dictates comprehensive comparability and immunogenicity studies required on a class-by-class basis. This distinction is irrelevant to the present research, but bears noting. "Highly similar" does not mean identical.

[137] See European Medicines Agency, 'Marketing Authorisation' and European Medicines Agency and the European Commission, 'Biosimilars in the EU: Information Guide for Healthcare Professionals' (2017). Additional medicines centrally regulated by the EMA include treatments for HIV, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune diseases, viral diseases, biotechnology products, advanced therapy medicines (e.g. gene therapy), and orphan medicinal products. Given this broad mandate, the EMA has become the predominant route for obtaining marketing authorization for new drugs in the EU.

Formal consideration of a biosimilars approval pathway began in the EU as early as 2001.[138] In 2003, consideration of "similar biological medicinal products" were first incorporated into the EU's market authorization provisions,[139] and the first biosimilar review guidance document – the hallmark for the development of approaches around the world – was adopted in 2005.[140] Biologic and biosimilar applications are submitted and assessed by the EMA's Committee for Medicinal Products for Human Use ("CHMP"). The CHMP provides initial assessments for marketing authorization of new medicines that are ultimately approved centrally by the EMA.[141]

In its submission to the CHMP, a biosimilar applicant must establish that the biosimilar is highly similar in functionality (biologic activity) and that there are no clinically meaningful differences in terms of safety, quality and efficacy in comparison to the reference biologic. In doing so, the biosimilar applicant is permitted to rely on the data and evidence upon which the reference biologic's approval was predicated, thereby creating an abbreviated pathway to authorization that avoids the unnecessary, as well as costly and unethical, repetition of clinical trials already establishing the safety and efficacy of the reference biologic. As part of these obligations, biosimilar applicants must provide comprehensive non-clinical product-by-product bioanalytic and manufacturing assessments, as well as clinical evidence to establish similarity.

At the outset, the EU's pioneering approach was acknowledged because it created a comprehensive regulatory framework, but the implications of such an abbreviated pathway in Canada and the US were wider reaching.

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[138] European Medicines Agency. Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 17 December 2003. EMEA/CPMP/3097/02/Final [homepage on the Internet]. 2003 Dec 22 [cited 2015 Aug 4]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003963.pdf

[139] Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. J Eur Union. 2003;L159:46-94.

[140] Agency, Guideline on Similar Biological Medicinal Products. October 30, 2005.

[141] EMA's evaluation and assessment procedure is compulsory for human medicines such as biosimilar products, orphan designated medicines, genetic engineered drugs, advanced therapy medicines such as gene therapy, and cellular therapy.

Ultimately, the abbreviated framework that Canada adopted was similar to the EU's approach. Of equal importance to this research, Canada also linked the biosimilar regulatory assessment to biologic patent consideration in the same way that the regulatory assessment of a generic pharmaceutical is linked to the brand's patents, data exclusivity and now their *sui generis* rights. In Canada, the standard for assessing biosimilars in reference to reference biologics is identical to the EU's approach (as well as the US' described below). Drugs,[142] including pharmaceuticals and biologics, are regulated by Health Canada pursuant to the Canadian Food and Drugs Act[143] and Food and Drugs Regulations,[144] and are subject to the *Patented Medicines (Notice of Compliance) Regulations*,[145] and the Canadian *Patent Act*.[146] The Biologics and Genetic Therapies Directorate ("BGTD"), a directorate of the Canadian regulatory authority Health Canada, is responsible for the review and assessment of all submissions related to biologics and biosimilars.[147] Health Canada uses the term biosimilar to describe "a biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product."[148]

No company may sell or advertise a drug in Canada without first obtaining a Notice of Compliance ("NOC") from Health Canada.[149] To obtain a NOC, an applicant must file a drug submission – new or supplemental new drug submission (NDS or SNDS), abbreviated or supplemental abbreviated new drug submission (ANDS or SANDS) – with Health Canada submitting comprehensive information as prescribed by legislation and

[142] Canadian Food and Drugs Act s. 2. Section 2 of Canadian *FDAct* provides that the term "drug" includes any substance of mixture of substances manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, (b) restoring, correcting or modifying organic functions in human beings or animals, or (c) disinfection in premises in which food is manufactured, prepared or kept.
[143] Id. at.
[144] Food and Drug Regulations, C.R.C., c. 870.
[145] Canadian PM(NOC) Regulations s. 49.
[146] Canadian Patent Act.
[147] Canada, Guidance Document Information and Submission Requirements for Biosimilar Biologic Drugs 4. 2017.Specific regulatory requirements for biologics and biosimilars are set out in Division 4 of Part C of the *FDA Regs*.
[148] Health Canada Guidance Doc
[149] FDRegs. C.08.002(1)(a) and C.08.002(2).

policy. Biologics applications proceed by way of NDS (or SNDS) and, despite being an abbreviated assessment pathway based on biosimilarity, so do biosimilars.[150]

In Canada's abbreviated biosimilar pathway, the biosimilar applicant has the benefit of relying on a reference biologic that has previously been authorized on the basis of a complete quality, non-clinical, and clinical data package. As a result of this reliance, the biosimilar applicant must establish in its NDS the comparative similarity in the quality, safety and efficacy to the reference biologic.[151] Interestingly, Canada allows a biosimilar sponsor to rely on a Non-Canadian reference biologic.[152]

As is the case with the EMA/CHMP, Health Canada's BGTD will evaluate whether the biosimilar application demonstrates that, in comparison to the reference biologic, the biosimilar is highly similar, and there are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic. Health Canada's BGTD takes a step-wise approach to biosimilar application reviews, first requiring the biosimilar applicant to establish similarity based on structure and function (such as product stability, biological activities, physiochemical properties, immunochemical properties, purity and impurity profiles),[153] second moving on to non-clinical and clinical studies that may speak to toxicity or immunogenicity. The purpose of clinical studies is to establish that there are no clinically meaningful differences in efficacy and safety expected between the biosimilar and reference biologic.

Further, the biosimilar applicant (as well as the reference biologic holder) must demonstrate their ability to consistently manufacture the biosimilar as per its represented specifications. This assessment may also include onsite evaluation visits and laboratory testing conducted by Health Canada's BGTD.

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[150] As defined in C.08.001.1.
[151] Heath Canada Guidance
[152] Canada, Guidance Document Information and Submission Requirements for Biosimilar Biologic Drugs. 2017.
[153] Id. at, 6.

The US's approach to biosimilars culminated in the creation of an abbreviated regulatory pathway. However, unlike Canada, the US did not follow its existing brand/generic approach in crafting the link between the regulatory assessments of biosimilars and the biologic holder's patents. In terms of the regulatory framework, it is the Center for Drug Evaluation and Research (CDER) which is the agency of the US Government's Department of Health and Human Services within the FDA responsible for regulating biologics and biosimilars for human use[154] under applicable federal laws, including the *Public Health Service Act*[155] and also, since most biological products also meet the definition of "drugs", under certain provisions of the *Federal Food, Drug and Cosmetic Act*.[156] In broad strokes, the assessment approach in the US is highly similar to the EU's criteria of safety, efficacy and quality.[157] Like Canada, the US has a product-specific assessment approach where each biosimilar has its own approval requirements assessed in a stepwise manner which will include comprehensive bioanalytical comparisons, clinical studies and other study requirements as determined by the degree of similarity as well as any discernable bioanalytical differences.

In the context of generic pharmaceuticals, the *Hatch-Waxman Act*[158] enacted in 1984 established the legislative framework for generic manufacturers to obtain market authorization granted by the FDA through a new abbreviated pathway for the approval of new drugs, through the abbreviated new drug application ("ANDA") process.[159]

[154] §351(k)(3), §351(k)(5)(b)
[155] Public Health Services Act ("US Public Health Services Act")
[156] Federal Food, Drug and Cosmetic Act
[157] A key difference in the US is the creation of a dual abbreviated assessment framework in §351(k); in addition to a finding of "similarity", the FDA may also determine that a biosimilar is "interchangeable" with the reference biologic. See Sections 7001 through 7003 of the Patient Protection and Affordable Care Act Of 2010, Pub. L. 111–148. An interchangeable product may be substituted for the reference biologic without the intervention of the healthcare provider who prescribed the reference biologic. This has some serious implications for considerations outside of the scope of this present work that will directly impact the uptake of biosimilars after their launch on the market.
[158] Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Act"), Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified across various provisions of Titles 21 and 35 of the U.S. Code).
[159] Hatch-Waxman at §101.

However, no such pathway equivalent existed for biosimilars until relatively recently in 2010.[160]

Up until 2010, the regulatory assessment pathway for biosimilars seeking market approval was the new drug application ("NDA") pathway identical to the previously approved biologic.[161] In essence, the FDA's biosimilar approval process was a complete repetition – requiring the identical data and evidence – to the approval process that already resulted in the FDA granting approval to the biologic. In pharmaceutical parlance, there was no abbreviated ANDA-like pathway created for biosimilars until, after almost a decade of discussion,[162] the enactment in 2010 of the *Biologics Price Competition and Innovation Act* (US Biosimilars Act),[163] a subtitle of the *Patient Protection and Affordable Care Act* (US Affordable Care Act).[164]

The US Biosimilars Act, amended, among other provisions, §351 of the *Public Health Services Act* ("US Public Health Services Act"),[165] creating an abbreviated pathway for the FDA to assess biosimilars that are either biosimilar to or interchangeable with a previously licensed biologic product[166] through an abbreviated process pursuant to §351(k) by way of the Biologic License Application (BLA) procedure. Importantly, the abbreviated pathway created by the US Biosimilars Act is two pronged creating an approval pathway for biosimilars that are demonstrated to be biosimilar as well as interchangeable with a reference biologic.

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[160] Ohly & Patel, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, (2011). Decaire, et al., UNIVERSITY OF SAN FRANCISCO LAW REVIEW, 1032 (2012).
[161] Ohly & Patel, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, 472 (2011). Decaire, et al., UNIVERSITY OF SAN FRANCISCO LAW REVIEW, (2012).
[162] Ohly & Patel, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, 471-475 (2011).
[163] Biologics Price Competition and Innovation Act, 42 U.S.C. § 262 (2010).
[164] Patient Protection and Affordable Care Act Pub. L. 111-148, 124 Stat. 119 (2010) (codified across various provisions of Titles 26 and 42 of the U.S. Code).
[165] Public Health Service Act Pub.L. 78–410, 58 Stat. 682.
[166] Michael P. Dougherty, *The New Follow-On Biologics Law: A Section by Section Analysis of the Patent Litigation Provisions in the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 231(2010). See Sandoz Inc. v. Amgen Inc., 773 F.3d 1274, 1275 (Fed. Cir. 2014). Pursuant to §351 (k)(2)(a)(i-iv), the biosimilar must have the same mechanism of action, root of administration, dosage form, strength, and indications in the proposed labeling as the reference biologic.

Through the BLA biosimilarity pathway the biosimilar applicant must establish a high degree of similarity between the reference medicine and biosimilar which may include some inherent minor differences in clinically insignificant modifications or tolerable heterogeneity. In establishing biosimilarity, the biosimilar application must establish that there is no clinically meaningful differences in the safety, purity and potency (efficacy) in comparison to the reference biologic.[167] In doing so, the biosimilar applicant must conduct and submit non-clinical and clinical studies, such as bioanalytical studies showing that the biosimilar is highly similar to the reference biologic, animal studies assessing toxicity, as well as any clinical studies that may be required at the direction of the FDA.

2.5.3. Regulatory Triggers for Patent Linkages, Data Exclusivity and Additional IP Provisions

Understanding how biosimilars and biologics are regulated in Canada, as well as the US and EU, is key to appreciating the way in which the regulatory processes in each jurisdiction are designed to similarly intersect with the patent/IP clearance regimes, namely patent linkages, data exclusivity and additional IP provisions, mandated by their respective international obligations implemented in national legislation and regulatory frameworks. As previously alluded to, patent strategies are heavily influenced by patent linkage regimes. As will become apparent in this section and the coming chapters, a given biologic manufacturer's patent strategy has a material impact on the market authorization of biosimilars containing the same active therapeutic ingredient given its potential operative effect in the context of national patent linkage regimes, as well as additional patent-based or *sui generis* rights arising from eligible patents.

[167] See Zachary Brennan, *Updated: Biosimilars in the US: Panel Discusses Tricky Balance of Building the Market With Necessary Precautions* RAPS(June 20, 2016), *available at* https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2016/6/updated-biosimilars-in-the-us-panel-discusses-tricky-balance-of-building-the-market-with-necessary. Dr. Leah Christi of the US FDA's CDER explains in detail the FDA's approach and standards applicable to the regulation of biologics and biosimilars. See also Christi.

The patent strategies described in this chapter speak to the patent strategies that are influenced by biologic/biosimilar technology. The complexity of biologics and biosimilars have generally given rise to more patents claiming core inventions (product, formulation and use of the product) and patentable underlying development and manufacturing technology. Patent applications are usually filed at the outset of biologic development and may encompass inventions beyond just the biologic, but also touch on aspects of it development and manufacture. Given the lengthy regulatory process coupled with the "first to file" requirement, an effective loss of patent term results where much of the nominal 20-year patent term may be expired. In addition, a patent grants a right to exclude others from practicing an invention claimed in the patent, which would preclude a biosimilar not only from practically precluding others from competing on the market with a biologic that falls within the scope of the invention. As aptly demonstrated by the comprehensive, albeit narrow in scope, assessment of Jeffery Wu and Claire Cheng, this patent strategy yields filing multiple, overlapping patents with potentially overbroad claims that serve to obfuscate the patent landscape for a particular biologic referred to as "patent thickets", some of which may be eligible to be asserted in the context of patent linkage regimes.[168]

A comparative analysis of patent linkages is detailed in Chapter 4. However, it is critical to first understand how patent considerations are intertwined with the regulatory assessments of biologics and biosimilars. Turning first to patent linkages, these regimes are mandated by some treaty obligations requiring the linkage between the regulatory authorization process with the status of the reference biologic holder's patent(s) which must be addressed prior to a regulatory agency's grant of market authorization. In this way, the biosimilar applicant has to establish that it will not fall afoul of the reference biologic's applicant patents before they are infringed through practicing the claimed invention beyond the statutory early working exceptions. Alternatively, the biosimilar applicant must successfully invalidate any relevant patents, again, prior to being granted

[168] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019).

market authorization. This linkage was thought to balance against the benefits conferred by the early working exception afforded to biosimilar applicant allowing for the development of biosimilars during the term of the reference biologic holder's patent(s). One main differentiating factor between patent linkage regimes is the identification of the biologic holder's patent(s) that will need to be addressed, one way or another, by the biosimilar applicant prior to approval.

The underlying justification of the patent linkage regime is the restoration or compensation for harm arising from (1) the reference biologic holder/patentee's inability to practice its invention during the time it takes to get regulatory approval for the reference biologic and (2) the early working exception that benefits the biosimilar company by providing an exception to what would otherwise be infringement of the reference biologic holder's patent(s).

Turning next to data exclusivity, these regimes generally operate in the same way in Canada, the US and EU and are managed at the regulatory agency level. All biologics that come to the market have to undergo regulatory approval in Canada, the US and EU, respectively, based on evidence and data to establish the safety, effectiveness and quality control of a new biologic. This evidence and data is mandatory and must be submitted in order for the biologic applicant to obtain market authorization. This mandatory evidence and data can be relied upon by biosimilar applicants to produce alternative versions of the biologic to compete with the biologic on the market. Data exclusivity provisions provide some protections over the use and disclosure of the biologic applicant's evidence and data from a biosimilar applicants' reliance in two practical ways.

The first is a prohibition from the filing of a biosimilar application. Calculated from the first market authorization date, a reference biologic holder's evidence and data cannot be relied upon by a biosimilar applicant because the biosimilar's application will not be received by the relevant authority until the expiry of a prescribed period of time. In

short, the biosimilar applicant is precluded from filing its submission with the regulatory authority until the expiry of this period, namely the "filing prohibition" period.

The second exclusion is imposed on the regulatory agency's ability to grant market authorization, even if the biosimilar is approvable. Specifically, a biosimilar application making reference to a reference biologic and relying on its evidence and data may be assessed by the regulatory agency after the filing prohibition period, however, even if the assessment has been concluded favourably, the regulatory agency is precluded from granting market authorization/approval until the expiry of this second period, namely the "authorization prohibition" period.

The justification of data exclusivity provisions is to compensate the reference biologic holder from the harm arising from allowing a competing biosimilar with the ability to rely on information, evidence and data of information taking considerable effort to generate that the reference biologic holder was compelled to disclose for regulatory purposes.[169] It has been argued by various stakeholders that data exclusivity provisions are also necessary to encourage continuous innovation given that patents are usually filed at the outset of development and much of the nominal 20-year patent term is lost during the lengthy regulatory process. However, as explored in Chapter 5, data exclusivity has yet in play a role in the biologics/biosimilars realm.

It is important to note that data exclusivity is not related to patent considerations; patents do not protect data. Data exclusivity may be relied on by a reference biologic holder even where there is no patent protection on the biologic. Where a company has a comprehensive patent portfolio, the data exclusivity benefits are not engaged unless the period of protection extends beyond the patent term. Where data exclusivity protection becomes truly beneficial is where there is difficulty relying on the ability to assert a patent(s) in the event (1) of no patent protection, (2) a patent has been found not to be infringed, (3) a patent has expired, and/or (4) a patent is found invalid.

[169] Sandra Adamini, et al., *Policy Making on Data Exclusivity in the European Union: From Industrial Interests to Legal Realities*, 34 JOURNAL OF HEALTH POLITICS, POLICY AND LAW, 984 (2009).

Additional IP provisions fall generally within two categories: provisions that purport to affect the patent term such as patent term extension, restorations, and/or adjustments and those that mandate the creation of *sui generis* rights not directly related to patent rights but analogous to such rights in effect. As discussed in the context of Chapter 4's comparative analysis, these types of treaty obligations have domestically manifested through the creation of supplementary protection certificates in the EU and certificates of supplementary protection in Canada that are not themselves patent rights but are impacted by patent status. Mitigating the alleged undue delay arising from the lengthy regulatory assessment of a biologic is the purpose of these types of additional IP provisions. The justification is to lessen the unreasonable curtailment of the effective term of the patent due to the mandatory market authorization process.

The regulatory trigger for either patent term extensions or the assertion of *sui generis* rights does not operate to affect the filing of a biosimilar application for market authorization. However, these rights, if valid and subsisting, may operate to preclude the approval of the biosimilar. In this way, the biosimilar application may be compliant and approvable in all respects, but the issuance of the authorization or approval must wait until the expiry of the patent or sui generis rights term(s) and are no longer a bar to the biosimilar.

2.6. Summary of Chapter 2

Chapter 2 has laid the foundation for the justifications underlying the international and national therapeutic innovation strategy in Canada, the US and EU; public and commercial interest dictates that steps must be taken to promote the innovation of these therapeutic agents through a variety of channels, one of which is ensuring an appropriate balance between the protection of hard earned intellectual capital and facilitating competition through the encouragement of biosimilars, thereby cultivating an environment where innovation is continuously promoted.

The promise of biologics and biosimilars, their public health considerations and potential patient impact, is astounding; these macromolecules have opened a door to therapies that were not only previously unattainable, but also unknown.

The regulation of a biologic, aspects of which are acutely concerned with purity and impurities, is compounded by the reality that it is almost impossible to identically copy and exclusively isolate the target biologic or biosimilar which has patent and regulatory implications arising purely from the nature of their development and manufacturing technology.

While the term of a patent in Canada, the US and EU is 20 years from the date of filing, given that will likely take over a decade to get market authorization (not even a guaranteed outcome), a biologic's prospective exclusive commerciality is about half the patent term. Accordingly, the imperative for a biologic company is to coordinate patent and regulatory efforts through a life-cycle management strategy in order to maximize market exclusivity and, after the entry of competitive biosimilar, preserve market share. In terms of the patent and regulatory strategy for a biosimilar company, the patent and regulatory strategy is to attempt to have as much clarity on the risk profile of developing a competing biosimilar by assessing the patent landscape of the biologic and the technology surrounding the biologic as well as ascertaining any applicable exclusionary periods and/or rights extensions.

The product pipeline is of paramount importance making the intellectual capital that goes into the development of the pipeline the lifeblood of the company. Further, biologics and biosimilars are being developed in non-traditional ways by both traditional players (pharmaceutical companies) and newcomers (biologic and/or biosimilar companies) where the lines of "brand" vs. "generic" are blurred. It is the development and protection of their products' market authorization and penetration that is the driving force behind almost all strategic plans, including R&D, co-development agreements, assignment and licensing of technology, mergers & acquisitions, as well as

their lobbying efforts to effect legislative and policy change both at a national and international level.

CHAPTER 3. International Treaty Obligations Related to the Regulation and Protection of Biologics and Biosimilars

3.1. Introduction

A global shift occurred in the 80s in the international trade arena, the effects of which are still being felt all over the world decades later. That shift was the result of the integration of intellectual property rights considerations with the international trade agenda that was ultimately pressed upon the rest of the world by the more powerful, namely the US, EU and their pharmaceutical industries. Due to the pharmaceutical industry's steadily increasing economic value and its impact on healthcare outcomes, as well as ever-increasing spending, it was the gambit to strengthen pharmaceutical patent rights that drove the inclusion of intellectual property into the international trade agenda facilitated through international treaties and agreements.

International treaties embody agreements made between countries on important issues that are crafted to influence national economic, health, security and/or legal strategies. Such agreements relate to important geopolitical matters like land and water rights, defense, human rights, healthcare and trade to name a few. On this same scale of importance, intellectual property rights were thrust into the international trade agenda through the World Trade Organization (WTO) created in the 90s and it's *Agreement of Trade-Related Aspects of Intellectual Property Rights,*[170] the adoption of which was a requirement for entry into the WTO.[171] The choice of the WTO as the vehicle to drive the intellectual property into the international area is of particular note. As discussed in this chapter, the integration of intellectual property rights with the WTO as opposed to

[170] Agreement On Trade-Related Aspects Of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) Article.
[171] Peter Drahos, *The Universality of Intellectual Property Rights: Origins and Development*, PANEL DISCUSSION TO COMMEMORATE THE 50TH ANNIVERSARY OF THE UNIVERSAL DECLARATION OF HUMAN RIGHTS, s. 1 p 3, s. 2(ii),p 8. (1998).

other international groups like the World Intellectual Property Office was crafted to tie the enforcement of intellectual property compliance to the trade complex.

The creation of the WTO in the 1990s brought with it the global advancement of the intellectual property agenda through TRIPs which sought to bring harmony to patent laws among signatory countries. As well, TRIPs first mandated the adoption of protective legislation undisclosed data in respect of pharmaceutical products where the submission of data was made mandatory in order to receive market authorization.[172] Prior to TRIPs, Canada had entered into the 1992 *North American Free Trade Agreement*,[173] which first obliged Canada to adopt statutory data exclusivity and harmonize its patent laws to standards set out therein. Recently renegotiated and replacing North American FTA (1994), the *Canada-US-Mexico Free Trade Agreement*,[174] imposes patent linkage requirements, increased data exclusivity thresholds and introduces the concept of a *sui generis rights* regime, all of which was already mandated by the 2014 *Comprehensive and Economic Trade Agreement* between Canadian and the EU.[175] Negotiations were concurrently underway on the *Trans-Pacific Partnership*[176] which did not enter into force due to the US' refusal to ratify the agreement. The subsequently enacted *Comprehensive and Progressive Agreement for Trans-Pacific Partnership*[177] that rose from the ashes of the TPP was the reason significant amendment to Canada's patent linkage regime was made. Provisions related to data exclusivity and *sui generis* rights set out in TPP remain suspended but not off the table entirely.

[172] Agreement On Trade-Related Aspects Of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) at Article 39.3.
[173] North American Free Trade Agreement, 17 December 1992, Can. T.S. 1994 No. 2, 32 I.L.M. 289 (entered into force 1 January 1994).
[174] Canada-US-Mexico FTA (2020)
[175] Canada-EU FTA (2017).
[176] Trans-Pacific Partnership, unratified.
[177] Comprehensive and Progressive Agreement for Trans-Pacific Partnership. 2018.

The intellectual property/trade agenda integration, having significant economic and legal impact, extends to biologics and biosimilars and have progressively expanded in scope and stringency. The impacts of patent and regulatory international obligations related to biologics and biosimilars are felt by biologic innovators, biosimilar developers, and public and private healthcare industries, not to mention the patients these drugs were developed to treat. Unless there was intervention at the international treaty level, pharmaceutical patent rights were viewed by the US and the pharmaceutical industry as an increasing economic liability unless strengthened and widely adopted beyond US borders especially in light of the rise of the generic pharmaceutical industry in Canada.[178]

As explored in Section 2.5.3, national patent and regulatory linkages (patent linkages), data exclusivity and additional IP provisions (such as patent term extensions and *sui generis* rights) are integrated into the Canadian legislative and regulatory landscape applicable to biologics and biosimilars; the same holds true for the US and EU. However, much of the impetus for these provisions are founded on Canada's, as well as the US and EU's, international treaty obligations which, as discussed in this chapter, include remarkable protections that have progressively increased in scope and stringency. Accordingly, a detailed review of Canada's international treaty obligations related to the patenting and regulation of biologics and biosimilars is warranted and undertaken. This examination is necessary to give appropriate context to the way in which Canada has chosen to craft national legislation to fulfil its international obligation, in comparison to the choices made in the US and the EU undertaken in Chapter 4.

Turing first to TRIPs and the WTO, Section 3.2 sets the stage for the rise of intellectual property in the international trade agenda. Next, Section 3.3 explores the evolution of Canada's obligations rooted in the 1994 Canada-US FTA and culminating in the recently ratified Canada-US-Mexico FTA (2018). Similarly, Section 3.4 explores Canada's obligations founded in the Canada-EU FTA (2017) which had significant impact on

[178] Smith. March 30, 2000.

Canada's patent linkage system converting the patent litigation process from an *in personam* summary application proceeding to an *in rem* patent action with time limits. Finally, we explore in Section 3.5 the CPTPP (2018) which to date represents some of the most current positions of the US and its biopharmaceutical industry in terms of how patent linkages, data exclusivity, and additional IP provisions should be crafted, despite the fact that it is no longer a signatory to the agreement.

As we will see, the intellectual property provisions pushed by the international trade agenda were developed over time and through heavy influence from the US, EU and multi-national pharmaceutical industry, which begs the question of whether these international obligations are detrimental to the approval and access of biosimilars in Canada. What becomes subsequently apparent is a trend of increasing protections imposed on signatories to these international treaties – a ratcheting up of the type, complexity and duration of protections. As will be examined in Chapter 4 and 5, this trend was mirrored in Canada and has detrimentally impacted the authorization and adoption of biosimilars in Canada.

3.2. Overview and Context of International Treaties – Setting the TRIPs Stage

No other international treaty has had as significant an effect on the internationalization of intellectual property obligations than the WTO's TRIPs. TRIPs laid the foundation for subsequent international agreements promulgating international treaty obligations in respect of the regulation of biologics/biosimilars and related patent/IP considerations. These treaties include the *North American Free Trade Agreement*, [179] recently renegotiated and to be replace by the *Canada-US-Mexico Free Trade Agreement*,[180] the

[179] North America FTA (1994).
[180] Canada-US-Mexico FTA (2020).

Comprehensive and Economic Trade Agreement between Canadian and the EU,[181] the *Comprehensive and Progressive Agreement for Trans-Pacific Partnership.*[182]

Set out below at Table 3 are the signatories to each respective treaty (Contracting Parties) and the date that these treaties were signed and came into force.

TABLE 3 – RELEVANT INTERNATIONAL TREATIES AND THEIR RESPECTIVE CONTRACTING PARTIES

Agreement	Contracting Parties	Date Signed	In Force
TRIPs	Canada, US, EU Total of 164 Countries	April 15, 1994	January 1, 1995
CUSFTA	Canada and US		January 1, 1989
NAFTA	Canada, US, Mexico		January 1, 1994
CUSMA	Canada, US, Mexico	November 30, 2018	July 1, 2020
CETA	Canada and the EU[183]	October 30, 2016	September 21, 2017
CPTPP	Canada, Australia, Japan, Mexico, New Zealand, Singapore, Vietnam (Not yet in force in Brunei Darussalam, Chile, Malaysia, Peru)		December 30, 2018

Given its significance as the foundation for the internationalization of intellectual property, inquiry into the history and development of the WTO's TRIPs agreement is warranted in order to properly set the stage for the treaties that came after. The emergence of the WTO in 1994 marked a new beginning in international trade and economic relations, decades in the making and built upon efforts stemming back to the

[181] Canada-EU FTA (2017)
[182] CPTPP (2018)
[183] EU Member States: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden

unrealized conceptualization of the International Trade Organization in 1948.[184] One of the main pillars of the WTO's framework was the creation of TRIPs which represented the transition of intellectual property rights as predominantly national considerations to multilateral arenas at the behest of, among others, the US, EU and their pharmaceutical industries.[185] The development and implementation of TRIPs and what flowed in the time that came after is a topic that is both broad and deep; it provides important context as the starting point of international obligations related to the patenting and regulation of biologics and biosimilars and their progression and proliferation through subsequent international agreements. A comprehensive analysis of the history and global progression of TRIPs provisions is outside of the scope of this research. However, an overview of the history and political context of TRIPS, initial TRIPs obligations, the progression and spread of enhanced or "TRIPs-plus" and the countries and industry players that were motivated to entrench intellectual property rights into the trade agenda will provide the necessary context for this research.

The motivations that resulted in the desire to tie IP to trade lay with the pharmaceutical industry's dissatisfaction with WIPO and the Paris Convention as the vehicles to strengthen intellectual property protection in other countries. In the late 1970s, the United States Patent and Trademark Office, encouraged by the US pharmaceutical industry, requested a conference to discuss the revision to the Paris Convention which was rejected by WIPO.[186]The US' efforts then turned to the international trade apparatus; by coupling patent considerations with the trade agenda, mandatory minimum standards could be tied to effective enforcement mechanisms.

Dr. Peter Drahos has helpfully characterized the historical development of international intellectual property into three periods, the last of which, namely the global period, provides insight into the inclusion of intellectual property into the international trade

[184] https://www.wto.org/english/thewto_e/whatis_e/tif_e/fact4_e.htm
[185] Charles McManis, *Teaching current trends and future developments in intellectual property*, TEACHING OF INTELLECTUAL PROPERTY: PRINCIPLES AND METHODS (2008).
[186] THE MAKING OF THE TRIPS AGREEMENT: PERSONAL INSIGHTS FROM THE URUGUAY ROUND NEGOTIATIONS 297 (Jayashree Watal & Antony Taubma eds., World Trade Organization. 2015).

agenda.[187] The hallmark of the global period is the US-driven, systematic intertwining of intellectual property rights with international trade agreements in the 1980s.[188] During that time, the US made a series of amendments to its international trade legislation to incorporate intellectual property into its trade agenda in response to pressure from the US pharmaceutical industry. [189] These amendments empowered the trade apparatus of the US government to include intellectual property into its program of "rehabilitation" of countries identified as having trade practices that were detrimental or harmful to US held intellectual property rights, including the patent rights of the pharmaceutical industry.[190] The remedial efforts included negotiation of bilateral agreements with the offending countries where, in the case of recalcitrant countries, the threat of trade sanctions loomed. This was in response to the movement in countries like Canada[191] where a generic pharmaceutical industries were developing and posed an increasing threat to brand pharmaceuticals' global profits.[192] Thus, during the 1986 Uruguay Round of trade talks leading up to the Marrakesh Declaration, the US-led initiative to link intellectual property with trade was spearheaded by key industry players, namely lobbyists from the US film and pharmaceutical industries whose lifeblood rests in their intellectual capital as expanded upon below.[193]

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[187] Drahos, PANEL DISCUSSION TO COMMEMORATE THE 50TH ANNIVERSARY OF THE UNIVERSAL DECLARATION OF HUMAN RIGHTS, s. 1, p 3. (1998).

[188] Id. at, s. 1 p 3, s. 2(ii),p 8.

[189] FREDERICK M. ABBOTT, THE INTERNATIONAL INTELLECTUAL PROPERTY SYSTEM : COMMENTARY AND MATERIALS (Thomas Cottier & Francis Gurry eds., The Hague
Boston : Kluwer Law International. 1999).
See also, Sisule F. Musungu & Graham Dutfield, Multilateral greements and a TRIPS-plus world: The World Intellectual Property Organization (WIPO) (Quaker United Nations Office (QUNO) Ottawa: TRIPS Issues Papers #3 ed., 2003).

[190] Drahos, PANEL DISCUSSION TO COMMEMORATE THE 50TH ANNIVERSARY OF THE UNIVERSAL DECLARATION OF HUMAN RIGHTS, s. 2(iv) p 10 (1998).

[191] Brazil, Argentina, Mexico and the Andean Pact.

[192] Drahos 2002, at 9.

[193] Drahos, PANEL DISCUSSION TO COMMEMORATE THE 50TH ANNIVERSARY OF THE UNIVERSAL DECLARATION OF HUMAN RIGHTS, s. 2(iv) p 10 (1998). Laurence R. Helfer, *Regime shifting: the TRIPs agreement and new dynamics of international intellectual property lawmaking.(Agreement on Trade-Related Aspects of Intellectual Property Rights)*, 29 THE YALE JOURNAL OF INTERNATIONAL LAW (2004). Drahos, PANEL DISCUSSION TO COMMEMORATE THE 50TH ANNIVERSARY OF THE UNIVERSAL DECLARATION OF HUMAN RIGHTS, 10 (1998).

Since its inception and in the decades following, the enactment and implications of TRIPs is the source of a considerable amount of academic engagement and criticism.[194] This is due to its controversial development which was regarded as the "most contentious and anomalous component of the Uruguay Round" of trade negotiations.[195] To say that TRIPs was, and remains, a polarizing instrument is an understatement.[196] Peter Sutherland, GATT Director-General, characterized it as "the greatest trade agreement in history";[197] however, opponents view it as a mere "TRAP" to both the developed and developing countries.[198] A perspective that was scarce in the voluminous discourse, however, were first-hand accounts of those who were involved in the negotiations. An attempt to remedy this deficiency on the record was made in recent years and culminated in a book that, while published by the WTO, endeavors with varying degrees of success to provide a more informed and objective understanding of the TRIPs development from the perspectives of variously interested actors.[199]

The integration of the pharmaceutical industry in discussions to strengthen and internationalize patent protection began before the negotiations of TRIPs. In the mid-1970s when the US formed the Advisory Committee on Trade Policy and Negotiation with the purpose of advising the US President on trade issues, it is telling that this body was chaired by the CEOs of Pfizer and IBM. Ultimately, one of the goals of TRIPs was to extend established and stronger IP protections like those found in the US and EU to new and emerging economies for their entrenchment into domestic law. This was a goal assiduously sought by countries with strong pharmaceutical industries such as the US

[194] See prolific researchers such as Daniel Gervais, Peter Drahos, Peter Yu.
[195] G. Dunkley, The Free Trade Adventure: The WTO, the Uruguay Round and Globalization-A Critique, Zed Books, Third World Network, New York, 2000, at 69.
[196] M. Trebiloek and R. Howse, The Regulation of International Trade, 2nd edition, Rootledge, London, 1999.
[197] Statement by Peter Sutherland, GATT Director-General, in Dunkley, supra, at 3.
[198] D. Chisum, commenting on why the term TRIP was selected instead of "why isn't it 'TRAP', which might be more descriptive", Remarks by Professor Chisum, 22 Vanderbilt Journal for Transnational Law 2. 1989, 341 at 342.
[199] The Making of the TRIPS Agreement: Personal insights from the Uruguay Round negotiations 3-4. 2015. this account does not purport to be an authoritative history nor a guide to legal interpretation.[FN – Book at 3-4]

and Switzerland.[200] Ostensibly, the rationale behind this questionable agenda is that monopolistic regimes would provide the necessary incentive for technological innovation in order to spur social and economic progress.[201]

It is a trite proposition that the biopharmaceutical industry considers patents as a key aspect in the protection of its technology, a proposition that has been supported by surveys going back before the negotiation of TRIPs and carrying forward in the US and other countries.[202] Recall, this is also an industry engaged in comprehensive, sophisticated and expensive lobbying efforts. Thus, it should come as no surprise that the most active players – the key "*demandeurs*" – in the pharmaceutical lobby came from the US, EU, Japan and Switzerland,[203] namely, the countries reflected in Table 1 where all of the top pharmaceutical companies by revenue reside. A slightly altered group called the "quad" spearheaded the Uruguay Round, namely the US, EU, Japan, and also Canada. Canada's compulsory licensing regime was at odds with the others which, some TRIPs negotiators speculated, allowed it to play a moderating role against the other three's interests to protect its generic drug industry.[204] However, as is argued herein, that has not borne out in reality in respect of biologics and biosimilars.

TRIPs describes the minimum rights that member states must provide to patentees;[205] it establishes the minimum requirements upon which each state's national law can be built, however these "minimums" largely meant that Contracting States would have to strengthen their national IP laws.[206] Specifically, TRIPs requires member states to

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[200] Id. at, 80, 161.
[201] Diana D. McCall, *Stating the Obvious: Patents and Biological Material Note*, 2003 U. ILL. J.L. TECH. & POL'Y 239(2003).
[202] For a survey of the literature, see The economics of intellectual property: Suggestions for further research in developing countries and countries with economies in transition (Geneva: World Intellectual Property Organization, 2009), chapter 5.
[203] The Making of the TRIPS Agreement: Personal insights from the Uruguay Round negotiations 80, 297. 2015.
[204] Id. at, 5, 43, 86, 298.
[205] TRIPs, Part II, Section 5 of TRIPs, Articles 27 – 34
[206] Susy Frankel, *The Continuing Excesses of Trade Agreements and the Object and Purpose of International Intellectual Property*, 50 IIC - INTERNATIONAL REVIEW OF INTELLECTUAL PROPERTY AND COMPETITION LAW 523(2019).

provide patent protection for pharmaceutical inventions for at least 20 years from the date of filing necessitating a term increase in some states like Australia and New Zealand.[207] The requirement that patent protection must be available for both products and processes in all fields of technology was the cause of some debate, especially with Contracting States with compulsory licensing and/or generic pharmaceutical industry.[208] Indeed, some states only provided for product patents after a transition period (Spain, Portugal and Greece) and Canada did not provide product patents until 1993.[209] Member states do have the discretion to refuse patent protection on the basis of "*ordre public*" or morality. [210] In Canada, such an exception on the basis of morality does not statutorily exist. Arguably, the "morality" consideration which has roots in the US common-law, has been rejected given its statutory omission.[211]

TRIPs provides that WTO States may also exclude from patent protection inventions directed to diagnostic, therapeutic and surgical methods, plants and animals (other than microorganisms), and biological processes for the production of plants or animals (other than microbiological processes).[212]

This purported harmonization of intellectual property laws was criticized as a "one-size-fits-all legal standards that ignored local needs, national interests, technological capabilities, institutional capacities and public health conditions."[213]

As a WTO agreement, TRIPs ties intellectual property considerations to other trade issues also integrate their enforcement mechanisms which tend to have stronger "teeth". For many countries, TRIPs established an international intellectual property

[207] TRIPs at Article 33. [Book at 313]
[208] TRIPs at Article 27.
[209] Book Field 139
[210] Agreement On Trade-Related Aspects Of Intellectual Property Rights, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) Article 27.2.
[211] Margo A. Bagley, *Patent first, ask questions later: morality and biotechnology in patent law*, 45 WILLIAM AND MARY LAW REVIEW (2003).
[212] TRIPs at Article 27.3
[213] Peter K. Yu, *International Enclosure, the Regime Complex, and Intellectual Property Schizophrenia The International Intellectual Property Regime Complex*, 2007 MICHIGAN STATE LAW REVIEW (2007).

framework that Contracting States were forced to accept along with those strong enforcement teeth.[214] If a state like Canada wanted to play in the sandbox with the rest of the world, it had to accept all of the rules imposed by the trade agenda to have access to all the new toys, including TRIPs' intellectual property obligations which, by stepping foot into the sandbox, are now enforceable through the international trade apparatus of the WTO.[215]

TRIPs represented an expansion of patent protection that states were obliged to adopt,[216] the negotiations of which were the most complex and contentious issues on the table.[217] It is clear that the minimum requirements that TRIPs has created is not a "minimum" at all. Further, this fictional minimum has been rapidly and progressively increasing with each bilateral and multilateral agreement that imposes upon signatory states enhanced or "TRIPs-plus" provisions.

The American political environment and international trade/intellectual property agenda has systematically applied pressure on its trading partners – and they have not exactly been quiet about these goals. The *US Trade Act of 2002* states:

> [t]he principal negotiating objectives of the United States regarding trade-related intellectual property are … to further promote adequate and effective protection of intellectual property rights, including through… ensuring that the provisions of any multilateral or bilateral trade agreement governing intellectual property rights that is entered into by the United States reflect a standard of protection similar to that found in United States law…[218]

Post-TRIPs, pressures and additional bilateral and multilateral agreements pushed by the US has encouraged not only accelerated the adoption of TRIPs minimum patent

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[214] Helfer, THE YALE JOURNAL OF INTERNATIONAL LAW, (2004). See also, Peter K. Yu, *The Objectives And Principles Of The Trips Agreement.*, 46 HOUSTON LAW REVIEW (2009).
[215] Peter Drahos, *When the Weak Bargain with the Strong: Negotiations in the World Trade Organization*, 8 INTERNATIONAL NEGOTIATION (2003).
[216] Helfer, THE YALE JOURNAL OF INTERNATIONAL LAW, (2004).
J. H. Reichman, *Universal Minimum Standards of Intellectual Property Protection under the TRIPS Component of the WTO Agreement Symposium: Uruguay Round - GATT/WTO*, 29 INTERNATIONAL LAWYER (ABA) (1995).
[217] Book Field 139
[218] 19 USC s. 3802(b)(4)(A) (2004).

standards, but also TRIPs-plus standards. Essentially, the incorporation of patent protection standards and the US industry influence in the WTO served to benefit private business interests to the detriment of promoting access to innovation.[219]

An example of a TRIPs-plus accelerated adoption strategy pertinent to the present investigation is TRIPs is the obligation for Contracting States to protect undisclosed data. The original wording of the protection of undisclosed data in Article 39.3 of TRIPs does not represent what we have come to know as data exclusivity provisions. The obligation imposed by Article 39.3 of TRIPs provides that states are obliged to ensure protection against unfair commercial use and disclosure of test or other data as follows:

> Article 39.3. Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

Thus, two specific obligations are imposed related to use and disclosure. First, for data that is required to be submitted as a condition of the market authorization of a new chemical pharmaceutical product, said data requiring considerable effort to generate, WTO Contracting Parties "…shall protect such data against unfair commercial use."[220] Second, Article 39.3 provides WTO States "…shall protect such data against disclosure…" except where disclosure is necessary to protect the public, "…or unless steps are taken to ensure that the data are protected against unfair commercial use."[221] However, none of the language in this article implies that there should be any prohibition on the filing of submission or delays in the grant of market authorization. Simply put, this language

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[219] A. Samuel Oddi, *TRIPS--Natural Rights and a Polite Form of Economic Imperialism American Association of Law Schools' Intellectual Property Section's Symposium on Compliance with the TRIPS Agreement*, 29 VANDERBILT JOURNAL OF TRANSNATIONAL LAW, 424 (1996).
Stephen Barnes, *Pharmaceutical patents and TRIPS: a comparison of India and South Africa.(Agreement on Trade-Related Aspects of Intellectual Property Rights)(Symposium: The Law and Social Reform)*, 91 THE KENTUCKY LAW JOURNAL 917, 917 (2003).
[220] TRIPs at Article 39.3.
[221] TRIPs at Article 39.3.

refers to the protection of data from "unfair commercial use", the lack of definition of which caused the US some consternation during the negotiations,[222] and required "steps" to be taken to protect disclosure in the event it is necessary to "protect the public" – all of which is profoundly ambiguous or, given that this was by design, characterized as "constructive ambiguity".[223] There is no exclusivity granted by this provision to the data.[224] Further, there is no fixed period of time specified in Article 39.3, however (and peculiarly) a draft version did specify a time period of "generally no less than five years…"[225] It is unclear what a state was supposed to be doing in that "no less than five years" period of time. However, the TRIPs-plus provision that spawned from Article 39.3 of TRIPs made the inclusion of a timeframe make sense. Well before the recent Canada-US-Mexico FTA (2020), new, more detailed data exclusivity provisions dictating filing prohibition periods and authorization prohibition periods spread through bilateral agreements between the US and other countries where the bargaining power is usually high disproportionate.[226]

In this way, states got foisted into the sandbox through side-dealing resulting in bilateral and multilateral agreements designed to accelerate the adoption of TRIPs minimum patent standards which have been succinctly described by Peter Yu as TRIPs-plus provisions, TRIPs-extra provisions, and TRIPs-restrictive provisions.[227] As aptly described by Drahos, the US and EU trade apparatus uses bilateral agreements to ratchet up the harmonization of intellectual property rights to ensure they are linked to the trade agenda and embody at a minimum the TRIPs standards regardless of any existing

[222] Book field at 143-144
[223] Yu, MICHIGAN STATE LAW REVIEW, (2007).
[224] Piergiuseppe Pusceddu, *Assessing Access to Medicines in Preferential Trade Agreements: From the Trans-Pacific Partnership to the Comprehensive and Progressive Agreement for Trans-Pacific Partnership*, 49 IIC - INTERNATIONAL REVIEW OF INTELLECTUAL PROPERTY AND COMPETITION LAW 1048(2018).
[225] Lawrence A. Kogan, The U.S. Biologics Price Competition and Innovation Act of 2009 Triggers Public Debates, Regulatory/ Policy Risks, and International Trade Concerns, 6 Global Trade & Customs J. 513, 513 (2011)
[226] See enhanced TRIPS-plus data exclusivity provisions in the following FTAs: US-Australia (2005), US-Bahrain (2006), CAFTA-DR (2006-2009) between US and certain central American states; US-Chile (2004), US-Columbia (pending); US-Korea (2012); US-Oman (2009); US-Panama (2011); US-Peru (2009); US-Singapore (2004); Source: https://ustr.gov/trade-agreements/free-trade-agreements
[227] Yu, MICHIGAN STATE LAW REVIEW, 12 (2007).

transition periods in order to advance the patent agenda extending the TRIPs standard and accelerating the otherwise prescribed transition period.[228]

We now turn to how TRIPs has influenced the following international treaties. Prior to receiving market authorization, the following international treaty obligations mandate that Canada provide for national legislation and policies to mitigate against the delays in the regulatory market authorization process and the costs associated with developing these complex therapeutic agents, namely patent linkages, data exclusivity and additional IP provisions which include patent term extensions and *sui generis* rights. With this context, the remainder of the analysis of the treaty obligations arising from the following international treaties is now appropriately situated in light of the TRIPs evolution set out above.

3.3. Canada-US Free Trade Agreement (1989), North American Free Trade Agreement (1994), and Canada-US-Mexico Free Trade Agreement (2020)

Canada and the US began negotiating a free trade agreement in the mid-80s resulting in the Canada-US FTA (1989) that came into force on January 1, 1989. This agreement was superseded by the North America FTA (1992) which included Mexico and came into force on January 1, 1994.

It is important to keep in mind the political backdrop during this time. As noted above, the Uruguay Round negotiations was underway in the mid-80s. It would have been reasonable for the US and Canada to have left the contention issue of intellectual property on the table in Canada-US FTA (1989) in 1989 given the context set out in the treaty notes:

> During the course of the negotiations, the two governments worked on an overall framework covering the protection of intellectual property rights (trademarks, copyright, patents, industrial design and trade secrets). In the end, a substantive chapter was dropped. Nevertheless, in Article 2004, the two governments agree to continue to

[228] Drahos at 21.

> cooperate and work toward better international intellectual property rules, particularly in the Uruguay Round of Multilateral Trade Negotiations where a working group on trade-related intellectual property issues has been established.

A wider conversation about international trade and intellectual property rights was already occurring at the GATT/WTO level; indeed the North American FTA (1994) could be considered as one of the testing ground for the US strategies linking intellectual property rights to its international trade agenda given that effectively identical provisions related to patents ultimately ended up in TRIPs.

As was the case in TRIPs, both the North American FTA (1994) and Canada-US-Mexico FTA (2020) create minimum standards.[229] Similar to TRIPs, the North American FTA (1994) sought to harmonize many fundamental aspects of patent law applicable to biologics and biosimilars. This reiteration of the harmonization of patent law includes the principle that patentable subject matter encompasses all fields of technology, provided the invention is new, useful and non-obvious,[230] while continuing to provide for exceptions from patentability of methods of medical treatment, plants and animals (other than microorganisms) and essentially biological processes for their production, as well as "order public" and "morality" exceptions.[231] Canada-US-Mexico FTA (2020) also requires that Contracting Parties confirm that patents are available for inventions claiming, products, new use for known products, new methods for using a known product, or new processes of using a known product,[232] and provides for a one year grace period for public disclosure emanating from the patentee.[233]

Canada-US-Mexico FTA (2020) reiterates many of the harmonizing legal principles using TRIPs and the North American FTA (1994) as the foundation, and expands upon them.[234]

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[229] North American FTA (1994), Article 1702; Canada-US-Mexico FTA (2020) at Article 20.5 para 2.
[230] North American FTA (1994), Article 1709, para 1, Canada-US-Mexico FTA (2020) at Article 20.36
[231] North American FTA (1994), A 1709, para 2 and 3, Canada-US-Mexico FTA (2020), Article 20.36 at para. 2, 3.
[232] Canada-US-Mexico FTA (2020), Article 20.36 at para. 2;
[233] Canada-US-Mexico FTA (2020), Article 20.37.
[234] Many of these expanded international treaty obligations fall outside of the scope of the present work, but briefly include the creation of an intellectual property rights committee (Article 20.14), obligation of cooperation and work product sharing in respect of patent prosecution (Article 20.15, 20.16).

Canada-US-Mexico FTA (2020) represents a significant advancement of treaty obligations on Contracting Parties in respect of biologics and biosimilars by increasing the threshold of data exclusivity, mandating the implementation of a patent linkage systems (even if already existing in Contracting Parties), and providing for additional IP Obligations such as patent term restorations or a *sui generis* mechanism to achieve the same goal (this obligation is mirrored in Canada-EU FTA (2017)as discussed below).

3.3.1. Patent Linkage Requirements in the Canada-US-Mexico FTA (2020)

TRIPs did not impose any treaty obligations related to the linkage of regulatory assessments of biosimilars with the clearance of the reference biologic holder's patent rights. Recall that patent linkages are mandated by some treaty obligations requiring linkage between the regulatory authorization process with patent considerations which must be addressed before a biosimilar is granted market authorization. In this way, the biosimilar applicant has to establish that it will not fall afoul of the reference biologic's applicant patents before they are technically infringed. Alternatively, the biosimilar applicant must successfully invalidate any relevant patents, again, prior to being granted market authorization. This linkage was thought to balance against the benefits conferred by the early working exception afforded to biosimilar applicant allowing for the development of biosimilars during the term of the reference biologic holder's patent(s).

While it did not impose any international treaty obligations related to patent linkages on Canada and Mexico in the North American FTA (1994), the US negotiated a number of multilateral and bilateral treaties in the mid-90s imposing patent linkage treaty obligations going beyond TRIPs on all but one country (Israel) out of 20.[235] Unsurprisingly, Canada-US-Mexico FTA (2020)'s patent linkage provision represents an

[235] US-Australia (2005), US-Bahrain (2006), CAFTA-DR (2006-2009) between US and certain central American states; US-Chile (2004), US-Columbia (pending); US-Jordan (2001); US-Korea (2012); US-Oman (2009); US-Panama (2011); US-Peru (2009); US-Singapore (2004); Source: https://ustr.gov/trade-agreements/free-trade-agreements

evolution of these types of provisions and establishes a comprehensive linkage between the regulation of biologics and biosimilars with the reference biologic's patent status.

Canada-US-Mexico FTA (2018) Article 20.50 entitled "Measures Relating to the Marketing of Certain Pharmaceutical Products" links the regulatory approval of a biosimilar with the patent status of a biologic approved in any Contracting Parties, or other territory.[236] Contracting Parties are required to provide a system that will require notice to be given to the reference biologic's holder that the biosimilar applicant is seeking marketing authorization, and to provide for sufficient time and access to judicial or administrative proceedings to seek remedies for potential and allegedly infringing acts that may arise from a grant of market authorization of the biosimilar.[237]

3.3.2. Data Exclusivity Requirements in the Canada-US-Mexico FTA (2020)

The North American FTA (1994)'s data exclusivity provisions are set out at Article 1711 and are operatively identical to Article 39.3 of TRIPs. However, while no period of time was specified in TRIPs, the North American FTA (1994) specifies a "reasonable period shall normally mean not less than five years from the date on which the Party granted approval to the person that produced the data for approval to market its product."[238] This reflects draft language of the North American FTA (1992) that was ultimately not included in the final North American FTA (1992) agreement. And, as discussed above, do not represent what has come to be known commonly as data exclusivity provisions until the TRIPs-plus agenda pushed them into the national legislation through bilateral and multilateral dealings.

Canada-US-Mexico FTA (2020) initially mandated a data exclusivity period of 10 years for biologics in respect of biosimilars entry.[239] However, and well after Contracting

[236] Canada-US-Mexico (2020) at Article 20.50.
[237] Canada-US-Mexico (2020) at Article 20.50 (1)(a) and (b).
[238] North American FTA (1994) at Article 1711.
[239] Draft Canada-US-Mexico FTA (2020), Article 20.49. 10 year data exclusivity period for biologics removed by the US.

Parties had signed the treaty, the provision was pulled from the agreement unilaterally by the US. This move was widely reported to be supported by House Democrats and industry organizations affiliated with generic and biosimilar manufacturers. Conversely, it was decried as an affront to the protection of American IP by brand/innovator industry organizations and seen as an erosion of the strong stance the US has taken against "pirates".[240]

What remains in the Canada-US-Mexico FTA (2020) is the limitation on the use and disclosure of protected data for a period of 5 years from the date of the marketing approval of the first biologic[241] in the Member State.[242] As well, where the first biologic data that is relied upon by the biosimilar applicant has been submitted in another Member State, then the data exclusivity period of 5 years runs from the date of the market authorization of the first biologic where the data relied upon was submitted.[243]

Further, the Canada-US-Mexico FTA (2020) provides a belt and suspenders provision making the coexistence of data exclusivity and patent rights explicit; where data exclusivity applies to a biologic, and that biologic is also covered by patent protection, the expiry of a patent term(s) does not alter the period of data exclusivity protection.[244]

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[240] See Andrew Segerman, Trump Administration and Speaker Pelosi Surrender Powerful Tool for Reining in Foreign Free Riding (Biotechnology Organization Institute December 10, 2019). Chester. Davis Jr, *USMCA Trade Agreement: A Victory for America's Patients* Association for Accessible Medicines(December 10, 2019), *available at* https://accessiblemeds.org/resources/press-releases/usmca-trade-agreement-victory-americas-patients. Zachary Brennan, *USMCA Drops Biologic Exclusivity Provisions for Mexico and Canada in Final Deal* RAPS(December 10, 2019), *available at* https://www.raps.org/news-and-articles/news-articles/2019/12/usmca-drops-biologic-exclusivity-provisions-for-me. Thomas Sullivan, *Biologic Exclusivity Provision Removed from USCMA Agreement* (December 17, 2019), *available at* https://www.policymed.com/2019/12/biologic-exclusivity-provision-removed-from-uscma-agreement.html. Rachel Cohrs, *Biologic exclusivity provision stripped from revised USMCA deal* (December 10, 2019), *available at* https://www.modernhealthcare.com/politics-policy/biologic-exclusivity-provision-stripped-revised-usmca-deal.

[241] While not specifically indicating that Canada-US-Mexico FTA (2020)'s Article 20.48 data exclusivity provision expressly includes biologics, the Article 20.49 Definition of New Pharmaceutical Product specifies that a "new pharmaceutical product" means a pharmaceutical product (which may include a biologic) that does not contain a chemical entity that has been previously approved in that Member State.

[242] Canada-US-Mexico FTA (2020), Article 20.48 at para. 1(a).

[243] Canada-US-Mexico FTA (2020), Article 20.48 at para. 1(b).

[244] Canada-US-Mexico FTA (2020), Article 20.51 of

3.3.3. Other Obligations Relevant to the Canada-US-Mexico (2020)

In addition to robust patent linkage and data exclusivity obligations, Canada-US-Mexico FTA (2020) also provides for patent term adjustments not necessarily tied to a biologic's patent status, but may in fact be so tied.

In respect of biologics that are subject to a patent, Canada-US-Mexico FTA (2020) obligates states to make a patent term adjustment available.[245] These adjustments created pursuant to this provision may be limited to a single adjustment for a biologic regardless of the number of patents, based only on the first marketing approval of the biologic in the state, and may be limited to a maximum of 5 years. [246]

Alternatively, a state may provide a *sui generis* period of protection that must attribute the rights conferred by the patent, but which in and of itself is an extension of the patent term and/or rights.[247] For such *sui generis* rights, states may limit this period of protection to 2 years. [248]

3.4. Comprehensive and Economic Trade Agreement (2017) – the Canada-EU FTA (2017)

Canada and the member states of the EU signed the Canada-EU FTA (2017) on October 30, 2016 which came provisionally into force on September 21, 2017.[249] This agreement was the result of almost a decade of discussions between Canada and the EU.[250]

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[245] Canada-US-Mexico FTA (2020), Article 20.46 at para. 2.
[246] Canada-US-Mexico FTA (2020), Article 20.46 at para. 3 and Footnote 40
[247] Canada-US-Mexico FTA (2020), Article 20.46 at para. 2 and footnote 39.
[248] Canada-US-Mexico FTA (2020), Article 20.46 at para. 3 and Footnote 40
[249] As of October 2019, 13 member states have notified the European Council of the completion of national ratification procedures for CETA. These Contracting Parties are Austria, Croatia, Czechia, Denmark, Estonia, Finland, Latvia, Lithuania, Malta, Portugal, Spain, Sweden, and the United Kingdom. Source: https://www.europarl.europa.eu/legislative-train/theme-a-balanced-and-progressive-trade-policy-to-harness-globalisation/file-ceta
[250] https://www.europarl.europa.eu/legislative-train/theme-international-trade-inta/file-ceta/05-2020

Given the overlap in the negotiations of both the Canada-EU FTA (2017) and the Canada-US-Mexico FTA (2020), it is interesting to see how the respective differences in the approaches to patent linkages, data exclusivity and additional IP provisions arose from the US' priorities versus those of the EU. The EU relies heavily on data exclusivity and *sui generis* protections, these types of provisions are robustly addressed and bolstered in the Canada-EU FTA (2017) as opposed to the Canada-US-Mexico FTA (2020) which does not contain similarly strong provisions. patent linkages, on the other hand, are only briefly addressed in Canada-EU FTA (2017); Canada does have existing domestic patent linkages, but the EU has none at all. However, given that the US and Canada have implemented comprehensive domestic patent linkage regimes, the Canada-US-Mexico FTA (2018) robustly addressed the inclusion of patent linkages.[251]

In terms of the Canada-EU FTA (2017), the contentious linkage issue, however, was the lack of appeal avenue in Canada, a new imposed obligation that will have lasting legislative, procedural, regulatory and jurisprudential impacts in Canada for some time.

3.4.1. Canada-EU FTA (2017) Patent Linkage Requirements

The patent linkage provisions in the Canada-EU FTA (2017) is short, but includes a requirement that has had a significant impact solely on Canada given that there is no patent linkage regime in the EU.

Article 20.28 of the Canada-EU FTA (2017) states

> **Patent linkage mechanisms relating to pharmaceutical products**
>
> If a Party relies on "patent linkage" mechanisms whereby the granting of marketing authorisations (or notices of compliance or similar concepts) for generic pharmaceutical products is linked to the existence of patent protection, **it shall ensure that all litigants are afforded equivalent and effective rights of appeal.** (emphasis added)

This provision steps beyond the Canada-US-Mexico FTA (2020)'s patent linkage requirements by requiring states to allow for equivalent and effective rights of appeal.

[251] Canada-US-Mexico at Article 20.51.

The practical implication of this obligation has been an overhaul of Canada's patent linkage regime that is detailed in Chapter 4. In short, amended Canadian PM(NOC) Regulations came into force in 2017 which shifted the previous *in personam* summary applications (without effective means of appeal) to full *in rem* actions resulting in final determinations on infringement and validity with rights of appeal.

3.4.2. Canada-EU FTA (2017) Data Exclusivity Requirements

The Canada-EU FTA (2017)'s data exclusivity provisions builds upon the international treaty obligations that all parties are bound to pursuant to Article 39.3 of TRIPs but provides timing specifications.

In addition to the restriction on use and disclosure,[252] Canada and EU states are precluded from allowing a biosimilar applicant to rely on the biologic applicant's data for a period of 6 years following the date of the biologic's market authorization without the biologic applicant's consent.[253] This provision precludes the "use" of the data in that the review of a biosimilar application that relies on a biologic applicant's data is prohibited for a period of 6 years from the date that the biologic was granted market authorization.

Further, Canada and EU states are precluded from granting market authorization for a biosimilar relying on the biologic applicant's data for a period of eight years from the date that the biologic was granted market authorization without the biologic applicant's consent.[254]

Taken together, a biosimilar application relying on a biologic's data is reviewable 6 years after the biologic's approval, but the biosimilar itself is not approvable until after eight years of the biologic's approval. Therefore, there is a two year period during which time a biosimilar application may be reviewed, but not approved.

[252] Canada-EU FTA (2017), Article 20.29 at para. 1 which are analgous to TRIPs Article 39.3.
[253] Canada-EU FTA (2017), Article 20.29 at para. 2(a).
[254] Canada-EU FTA (2017), Article 20.29 at para. 2(b).

3.4.3. Other Obligations Relevant to Canada-EU FTA (2017)

Canada-EU FTA (2017) has mandated the creation of a *sui generis* right that is analogous to patent rights as applied to biologic products, use or product by process patents.[255] Similar to the principles underpinning the *sui generis* protection obligated by Canada-US-Mexico FTA (2020), this type of provision is aimed at addressing the regulatory review delay causing loss of effective patent terms.

Contracting Parties are required to create this *sui generis* right to be applied to a first-time market authorized biologic in the Member State that has not yet been subject to a previously granted *sui generis* period of protection.[256] The biologic applicant must make an application for the *sui generis* protection within 60 days of either the first grant of market authorization for the biologic or the grant of an applicable patent.[257] The *sui generis* period of protection will begin upon the expiry of the applicable patent, if only one patent exists or, where more than one patent is applicable to this provision, upon the expiry of only one of said applicable patents.[258] The *sui generis* period of protection is calculated as the difference between the date of grant of the first marketing authorization less the filing date of the applicable patent less 5 years, but in no case (and notwithstanding any population testing incentives) shall the period exceed 2 to 5 years.[259]

The *sui generis* protection is constrained by the status of the applicable patent and may be revoked for a variety of reasons including, a finding of invalidity, lapse prior to its lawful expiry and narrowing of the claims to exclude eligible claims vis-à-vis the biologic.

[255] Canada-EU FTA (2017), Article 20.27 at para. 8.
[256] Canada-EU FTA (2017), Article 20.27 at para. 2.
[257] Canada-EU FTA (2017), Article 20.27 at para. 1 and 3.
[258] Canada-EU FTA (2017), Article 20.27 at para. 4.
[259] Canada-EU FTA (2017), Article 20.27 at para. 5 and 6.

3.5. Comprehensive and Progressive Trans-Pacific Partnership – the CPTPP (2018)

Negotiations resulting in the now defunct TPP were concluded on October 5, 2015 and the agreement was eventually signed on February 4, 2016 by all signatories. On January 30, 2017 the US advised the remaining signatories of its intention not to ratify the TPP which, due to an agreed upon GDP threshold, meant that the agreement could not enter into force.

Signatories to the TPP, less the US, then entered into further negotiations eventually leading to the CPTPP (2018) which concluded on January 23, 2018 and entered into force in Canada on December 30, 2018.[260] The CPTPP (2018) incorporates by reference many provisions of the TPP with the exception of some drastic, and ultimately suspended, intellectual property provisions in Chapter 18; these presently unenforceable international treaty obligations will remain suspended until all the parties decide otherwise.[261]

These contentious but suspended TPP provisions are not completely off the table; importantly, they may serve as indicators of the current thinking of some parties and their stakeholders, many of whom have stated their position publicly. While the parties may have delayed the discussion, these suspended provisions give us an indication of where the agenda is likely to develop in the future.

Accordingly, set out herein are the provisions related to patent linkages, data exclusivity and other treaty obligations related to biologics that were ratified in the CPTPP (2018), as well as the provisions that were left suspended as TPP relics; relics that could be revived anytime on consent of the parties.

[260] As of this date the CPTPP entered into force for Canada, Australia, Japan, Mexico, New Zealans, Singapore, and for Vietnam the agreement entered into force on January 14, 2019.
[261] CPTPP Article 2

3.5.1. Patent Linkage Requirements in the CPTPP (2018)

CPTPP (2018) ratifies a modified TPP provision related to patent linkages in Article 18.53.

Unsurprisingly, CPTPP (2018)'s patent linkage treaty obligations are identical to Canada-US-Mexico FTA (2020)'s Article 20.50 given that they were evolving at the same time through the same international trade negotiation channels. Like the Canada-US-Mexico FTA (2020), CPTPP (2018) establishes a comprehensive linkage between the regulation of biosimilars with the clearance of reference biologic holder's patent rights.

CPTPP (2018) states are required to provide a system where notice shall be given to the biologic's patent holder or licensee that the biosimilar applicant is seeking marketing authorization, and to provide for sufficient time and access to judicial or administrative proceedings to seek remedies for potential and allegedly infringing acts that may arise from a grant of market authorization of the biosimilar.[262] Notably, neither the Canada-US-Mexico FTA (2020) nor the TPP/CPTPP (2018) mandate and appeal avenue like the analogous requirement in the Canada-EU FTA (2017).

3.5.2. Data Exclusivity Requirements in the CPTPP (2018)

CPTPP (2018) does not impose any treaty obligations in respect of Data Exclusion on its signatory states.

The suspended TPP data exclusivity provision in Article 18.50 is structurally similar to the Canada-EU FTA (2017)'s data exclusivity provision, but the timeframes are more relaxed. In addition to the restriction on use and disclosure,[263] states are precluded from allowing a biosimilar applicant to rely on the biologic applicant's data for a period of 3

[262] CPTPP Article 18.53
[263] Suspended TPP at Article 18.50 at para. 1.

years (instead of Canada-EU FTA (2017)'s 5 years) following the date of the biologic's market authorization without the biologic applicant's consent.[264]

Further, states are precluded from granting market authorization for a biosimilar relying on the biologic applicant's data for a period of 5 years (instead of Canada-EU FTA (2017)'s 8 years) from the date that the biologic was granted market authorization without the biologic applicant's consent.[265]

The entirety of suspended TPP Article 18.51 specifically relates to data exclusivity applicable to biologics. This provision provides for a protection period of 8 years from the first market authorization grant of a biologic, increased from the 5 year period applicable to a pharmaceutical product pursuant to suspended TPP Article 18.50.1. As was the case during the negotiations of Canada-US-Mexico FTA (2020), a main point of contention was the data exclusivity provisions that called for a 10 year period of protection. Interestingly, the period of data exclusivity protection for a biologic called for in the TPP was 8 years, was subsequently suspended in the CPTPP (2018).

3.5.3. Other Relevant Obligations in the CPTPP (2018)

Other relevant provisions that harken back to the effort to harmonize patent laws through the international trade agenda culminating in TRIPs were restated in the TPP, but eventually suspended in CPTPP (2018).[266] The operative provisions impose on states begin with making patents available in any field of technology, on the basis of novelty, non-obviousness, utility and patentable subject-matter, generally maintaining the TRIPs-level of exceptions to and exclusions from patentability.[267]

Suspended TPP Articles 18.46 and 18.48 sets out the latest iteration of the constructs pushed by interested pharma-protective parties: patent term extension/restoration

[264] Canada-EU FTA (2017), Article 20.29 at para. 2(a)
[265] Canada-EU FTA (2017), Article 20.29 at para. 2(b)
[266] Suspended as per Article 2 of CPTPP: TPP Article 18.37 at para 2, last sentence of para. 4.
[267] CPTPP Article 18.37 at para. 1, 3 and 4.

provisions addressing, respectively, unreasonable delay due to patent prosecution or to compensate for regulatory delay. In fact and effect, the provision for unreasonable delay is similar to Canada's pre-existing treaty obligations, but are likely to be completely foreign for other states.

3.6. Summary of Chapter 3

Chapter 3 provides the historical and political context is necessary in order to understand the development of the ever-more harmonized international patent laws as time presses forward. For many countries, meeting TRIPs "minimum" standards caused widespread legislative changes which, by and large, were designed to bring national frameworks in line with the US and EU at the behest of industry groups heavily leveraged in intellectual capital, such as the pharmaceutical industry. Indeed, it was the pharmaceutical industries in the US, EU, Switzerland and Japan (incidentally the resident countries of the largest biopharmaceutical players) that sought increased patent protection. The intangible and inherently transient nature of information and technology, coupled with the requirement to regularly disclose this information to regulatory authorities, poses a significant challenge to this goal; however the US, EU and the intellectual capital dependent industries took up the challenge.

While an interesting story and a little bit of history is all well and good, the importance of this history lies in the implications of how the TRIPs "minimum standards" were implemented (willingly or otherwise) through the international trade agenda, namely the homogenization of strong patent protection potentially dampening innovation and development biologics and biosimilars.

Chapter 3's analysis of how the international treaty obligations related to biologics and biosimilars have changed since the widespread adoption of TRIPs in the mid-90s to the present with the implementation of two of the most significant trade agreements in recent time (Canada-EU FTA (2017) and CPTPP (2018)) is critical to understanding

Canada's national responses to these ratcheting obligations that will be address in Chapter 4. As is demonstrated in Table 4 below, a trend of increased complexity, restrictions and periods of protection is beginning to form. While the Suspended TPP provisions are not in force in Contracting Parties, these provisions do provide some guidance on what the US' expectations might look like moving forward.

TABLE 4 – SUMMARY OF INTERNATIONAL TREATY OBLIGATIONS RELATED TO PATENT LINKAGE, DATA EXCLUSIVITY AND ADDITIONAL IP PROVISIONS

Agreement	Patent Linkage	Data Exclusivity	Additional IP Provisions
TRIPs	No	Article 39.3 – Precursor Provision Period Not Specified	Harmonization of Patent Laws
CUSFTA	No	No	No
NAFTA	No	Article 1711 5 years from market authorization	TRIPs Harmonization of Patent Laws
CUSMA	Yes Comprehensive	5 year period of protection from the date of market authorization in the Member State or another Member State where the data resides 10 year limit applicable to biologics withdrawn unilaterally by the US	Patent Term Adjustment limited to a maximum of 5 years or *Sui generis* period of protection limited to 2 years
CETA	No obligation, but where patent linkages exist, the Member State is required to provide an appeal mechanism	6 years from the date of the first market authorization before a biosimilar is able to rely on the data in its submission 8 years from the date of the first market authorization before a biosimilar may be granted market authorization	*Sui generis* period of protection a minimum of 2 years
TPP	Yes Comprehensive	3 years from the date of the first market authorization before a biosimilar is able to rely on the data in its submission	Patent Term Adjustment – Undue delay arising from patent prosecution

		5 years from the date of the first market authorization before a biosimilar may be granted market authorization	Patent Term Adjustment - Undue delay arising from regulatory review
CPTPP	Yes Comprehensive	No – TPP Provision Suspended	No – TPP Provisions Suspended

Thus, the international foundation is appropriately laid which is critical to fully appreciate the implications of Canada's legislative choices that, as you will see in Chapter 4, has contributed to the dampening of biosimilar authorization in comparison to the EU.

CHAPTER 4. Comparative Legal Analysis of the Regulation of Biologics and Biosimilars and their linkages to Patent and IP Clearance in Canada, the US and EU

4.1. Introduction

As the previous chapters have demonstrated, the patenting and regulation of biologics and biosimilars addressed in international agreements are materially tied to the approval of biosimilars in Canada. However, these obligations examined in detail in Sections 4.2-4.4 do not specifically dictate the way in which signatories like Canada are required to domestically implement these obligations. This inherent discretion has led to a different approach in Canada, in comparison to the US and EU; differences that we will see in the following pages may serve to impede the number and timely entry of biosimilars on to the Canadian market.

The state-level integration of patent linkages, data exclusivity and other additional IP protections (patent term extensions, *sui generis* rights) has had consequences on the regulation of biologics and biosimilars because they have been largely developed in the context of pharmaceuticals and are still, by and large, in the process of maturing; it remains to be seen if these consequences were unintended, but some are without doubt unforeseen.

Accordingly, this chapter is a detailed investigation of Canada's patent linkages, data exclusivity provisions and other additional IP provisions directly or indirectly impacting the approval of biosimilars. This analysis will provide the necessary foundation for the further examination of how Canada, in comparison to the US and EU, has chosen to craft its domestic laws and regulations in an attempt to achieve balance between the incentivization of biologic innovation with the promotion of biosimilar development.

We first examine the integration of the biologic's patent considerations with the regulatory assessments of biosimilars, namely patent linkages. Patent linkages have influenced biologic and biosimilar manufacturers' patent and regulatory strategies. Canada's experience with patent linkage regimes, namely the Canadian *Patented Medicines (Notice of Compliance) Regulations*[268] is an example of how governments can forge the formal linkages between the patent status and regulatory approval of pharmaceuticals and biologics. Since 1984, the American system prescribed by the US's *Hatch-Waxman Act* (Hatch-Waxman Act)[269] established the abbreviated pathway to approval for pharmaceuticals which was then loosely analogized to biosimilars through the *Biologics Price Competition and Innovation Act* (US Biosimilars Act).[270] However, a recent ruling at the US Supreme Court[271] may release some of the pressure baked into the US Biosimilars Act's patent linkage regime until subjected to legislative reform. As well, biosimilar applicants are making significant use of post-grant patent challenge mechanisms before the USPTO and EPO. These are addressed in the context of the patent linkages due to their nexus to patent enforcement strategies.

Despite the harmonization and strengthening of patent laws in the EU, patent linkages are effectively non-existent; however, EU's data exclusivity protections have developed in scope and duration. The same could be said for data exclusivity in Canada (applying equally to pharmaceuticals as well as biologics), but is especially applicable to the US experience where data exclusivity terms for biologics stands at a astounding 12 years versus 5 years for pharmaceuticals.

In contrast to the contentious post-grant patent challenges, the less contentious additional IP provisions, such as the US' patent term extension and the *sui generis* rights (not identical, but analogous to patent rights) provided by Canada and the EU are next

[268] Canadian PM(NOC) Regulations.
[269] US Hatch-Waxman Act=
[270] Dov Hirsch, *The Riddle of the Mysterious Patent Dance Wrapped in an Enigma: Is the Patent Dance of the BPCIA Optional or Mandatory Notes*, 27 FORDHAM INTELLECTUAL PROPERTY, MEDIA & ENTERTAINMENT LAW JOURNAL (2016).
[271] Sandoz v Amgen, 137 S. Ct. 1664 (2017).

examined. There is, however, some nuance in the consideration of what is contentious vs. not contentious; the US' patent term extension regime is predominantly assessed and administered by the USPTO with input from the FDA, the decisions of which have not been challenged. In Section 4.4, we will examine the consequences of the implementation of different sui generis regimes mandated by Canada and the EU's international additional IP provisions. Specifically, a comparable situation plays out in the EU where the supplementary certificate of protection regime is administered by the regulatory body and rarely challenged. However, in Canada the Certificates of Supplementary Protection are tied to and litigated alongside the biologic's patents that are statutorily citable against the biosimilar's application.

Finally, the last section compares the number of biosimilars approved and launched on the market, if launched at all, in Canada versus the US and EU. As previously established, the EU has been at the forefront of biosimilar regulation and approval, the first biosimilar having been authorized in 2006. It was a decade later before the first biologic was approved in the US. While Canada adopted an assessment framework prior to the US, it has slightly lagged in its approval numbers, but interestingly its market launches are faring better than their American counterparts, the reasons for which necessitates further scrutiny in Chapter 5. Ultimately, we will see that the existence of patent linkages tying the biologic's patent status to the biosimilar's approval has had a dampening effect on the number of biosimilars approval as well as their launch into the Canadian market.

4.2. Patent Linkages to Regulatory Market Approvals in Canada, the US and EU

Patent linkages have progressively been mandated by treaty obligations as set out in Chapter 3. Where present, these obligations require that the national regulatory authorization process be linked with the status of the reference biologic holder's patent(s). These patents must be addressed prior to any grant of authorization by the national regulatory agency. In this way, the biosimilar applicant has to establish that it

will not infringe the reference biologic holder's patents. Alternatively, the biosimilar applicant must successfully invalidate any relevant patents, again, prior to being granted market authorization.

The following sections set out sequentially each of Canada, the US and EU's unique approach to patent linkages from one end of the spectrum where the process is fairly well characterized (Canada) to the other end of where linkages at the level of the EU does not exist. Interestingly, there is wide divergence on one critical issue that, as we will see in Chapter 5, has a profoundly detrimental effect on the clearance of the reference biologic holder's patents, namely their identification in advance of litigation.

4.2.1. Canada's Patented Medicines (Notice of Compliance) Regulations and the Canadian Patent List – To be (eligible), or not to be (eligible)

First enacted in 1993 since amended numerous times, Canada's *Patented Medicines (Notice of Compliance) Regulations* ("Canadian PM(NOC) Regulations") were crafted to link the Canadian drug regulatory approval process with an assessment of related patent rights,[272] but do not have an effect on the regulation or determination of public health and safety.[273]

These regulations were enacted to work in conjunction with Canada's version of the Bolar Exception, namely the early-working exception to patent infringement established by s.55.2 of the *Patent Act*.[274] Between its patent linkage regime and its early working exception, Canada sought a balance between a brand's patent rights and a generic's early-working exemption activities by linking Health Canada's ability to approve a

[272] Regulatory Impact Analysis Statement, (Patented Medicines (Notice of Compliance) *Regulations)*, *Canada Gazette II*, vol. 127, No. 6, 1993, p. 1383 at 1387. Regulations Amending the Patented Medicines (Notice of Compliance) Regulations, 2017, Regulatory Impact Analysis Statement, Canada Gazette Vol. 151, No. 28.
[273] Merck Frosst Canada Inc. v. Canada (Minister of Health) (1997), 80 C.P.R. (3d) 550 at 558.
[274] See *supra* Section 2.4.

generic drug to the patent status of the brand's reference drug product.[275] Specifically, Canadian PM(NOC) Regulations provide brands with an avenue to prevent generics from obtaining market authorization if their actions would otherwise result in patent infringement.[276]

While Canada's *PM(NOC)* proceedings predominately concern pharmaceutical litigation, they are applicable to biologics and biosimilars which, over time, will take greater prominence in the Canadian patent litigation landscape.

Recently, treaty obligations flowing from Canada-EU FTA (2017) obligated Canada to implement a right of appeal in the context of the Canadian PM(NOC) Regulations triggering a massive overhaul of Canada's patent linkage regime that came into force in 2017. These changes have a significant impact on pharmaceutical and biologics litigation in Canada, shifting away from the bicameral nature of pre-September 2017 pharmaceutical patent litigation. Previously, patent linkage proceedings were *in personam* summary applications without effective means of appeal ("PM(NOC) Applications"). Through the PM(NOC) Application, brands sought an order prohibiting Canadian authorities from issuing a Notice of Compliance in respect of a generic's submission and, once commenced, an automatic 24 month stay was granted pending the judgement on the application. This has been compared to an interlocutory injunction award without having to establish a prima facie case.[277]

An important distinction in these pre- September 2017 PM(NOC) Applications is that any appeal from these judgement, strictly applying solely to the parties before the Court, were considered moot in the event that the marketing approval was granted issued to

[275] Regulatory Impact Analysis Statement, *(Patented Medicines (Notice of Compliance) Regulations)*, *Canada Gazette II*, vol. 127, No. 6, 1993, p. 1383 at 1387.
[276] Amgen Canada Inc. v. Apotex Inc., 2018 FC 1078 at 19-23.
[277] Merck Frosst Canada Inc. v. Canada (Minister of National Health and Welfare), [1998] 2 S.C.R. 193, (per Iacobucci J.) at para. 33; cited in Ratiopharm Inc. v. Wyeth, Wyeth Canada and The Minster of Health, 2007 FCA 264 per Sharlow J.A. at para. 20. See also, Apotex Inc. v. Merck & Co. Inc., 2008 FC 1185 at paras 40-43

the generic/biosimilar.[278] The reference brand/biologic holder remaining option was to commence a subsequent traditional patent action for infringement pursuant to which the validity of its patents could be challenged in a forum where the finding would be applicable *in rem* because *res judicata* did not apply to the underlying PM(NOC) Application.[279]

That will no longer be the case. Post-September/2017, reference brand/biologic holders now advance full *in rem* actions resulting in final determinations on infringement and validity and having rights of appeal ("PM(NOC) Actions").[280] PM(NOC) Actions will apply to any notices of allegation, described below, served on a Brand after September 21, 2017. This represents a fundamental change to the process shifting the primarily paper-based application to a full patent trial with documentary production, oral examinations and viva voce evidence at trial. Judges will now be required to adjudicate final determinations on questions of patent validity and infringement, subject to a right of appeal, not simply whether the generic/biosimilar's allegations are justified.[281] In this way, the reference brand/biologic holder must defend the validity of its patent in a way that now will be binding beyond the present litigation while other potential biosimilar applications may be standing by in anticipation of the outcome. In the event that the validity of the reference brand/biologic holder's patents are held to be valid, *res judicata* will preclude additional challenges. However, invalidity findings, which were not a complete bar to subsequent PM(NOC) Applications with different generic/biosimilar parties, will now stand as final determinations, subject to appeal.

Importantly, there is an obligation for the reference biologic holder to identify patents claiming relevant inventive elements of the reference biologic upon its approval by providing a list of patents for inclusion on the Canadian Patent Register, this is an important regulatory trigger for the biologic which cannot be rectified if done

[278] Janssen v. Teva Canada Limited, 2015 FCA 36; Abbott Laboratories v. Apotex, 2007 FCA 368; Eli Lilly v. Novopharm, 2007 FCA 359
[279] Sanofi-Aventis Canada v. Novopharm Ltd., 2007 FCA 163 at para. 36
[280] Amgen Canada Inc. v. Apotex Inc., 2018 FC 1078 at 19-23.
[281] Amgen Inc. v. Pfizer Canada Inc., 2018 FC 1078 at para. 22-24

improperly.[282] The biosimilar applicant must address the listed patent(s) on the Canadian Patent Register, but only those listed as of the date of filing of the biosimilar's application; the patent list is effectively frozen as of the date of filing of the biosimilar's application.[283] When the generic/biosimilar applicant, the prescribed "second person", files an application making reference to a previously approved reference biologic, it must address all of the eligible patents on reference brand/biologic holder's patent list. If the generic/biosimilar applicant seeks to obtain a Notice of Compliance prior to the expiry of any of the reference biologic eligible patents, it must serve the reference brand/biologic holder with a Notice of Allegation ("NOA")[284] indicating either that it will wait until the expiry of the reference brand/biologic holder's listed patents or make one or more of the following allegations challenging the patent(s): (i) its biosimilar would not infringe any claim to the biologic or use of the biologics in the patent(s); (ii) the listed patent(s) are invalid or have expired; or (iii) the reference biologic who filed a patent list in respect of the drug is not the patentee nor has consent from the patentee to list the patents.[285] The 24-month prohibition from issuing a Notice of Compliance in respect of a second person's submission is maintained which significantly fast-tracks the Canadian patent litigation.[286]

If, after receiving the biosimilar applicant's Notice of Allegation, the reference biologic holder decides to challenge the biosimilar applicant's allegations, it must do so in accordance with the process set out in s. 6 of Canada's PM(NOC) Regulations within 45 days of service of the biosimilar applicant's Notice of Allegation, commencing a PM(NOC) Action in the Federal Court for a declaration that the making, constructing, using or selling of the second person's drug would infringe any patent or CSP that is the subject of the biosimilar applicant's allegation. Commencement of the PM(NOC) Action automatically triggers a 24 month stay prohibiting the Minister of Health from issuing a

[282] Canadian PM(NOC) Regulations;Government of Canada, Guidance Document Patented Medicines (Notice of Compliance) Regulations (Health Canada ed., May 11, 2018).
[283] PM(NOC) Regulations At. 5(4)
[284] PM(NOC) Regulations At s. 5.1., Guidance at s. 5.1
[285] PM(NOC) Regulations At s. 5.1., Guidance at s. 5.1
[286] Canadian PM(NOC) Regulations s. 7(1).

NOC in respect of the biosimilar. Importantly, if the reference biologic holder misses the 45-day deadline, the avenue to contest the biosimilar "second person" is forever closed.

The Canadian Patent Register contains a list of the reference brand/biologic's patents that the generic/biosimilar applicant is required to address in its Notice of Allegation and the subsequent PM(NOC) Action if brought by the reference biologic holder. This is a critical aspect in Canadian patent litigation because the universe of patents that may be asserted by the reference brand/biologic holder through the Canadian patent linkage regime is known. Only patents having a Canadian filing date prior to the filing date of the reference biologic's new, or supplemental, drug submission (NDS/SNDS) may be listed on the Patent Register[287] and a list of eligible patents must be filed at the time of filing the NDS/SNDS; patent lists submitted separately will be refused.[288] If an eligible patent is not yet granted, it must be listed within 30 days of issuance.[289] In order to be eligible for listing on the Patent Register, a patent must contain a claim to the medicinal ingredient, a claim for the formulation containing the medicinal ingredient, a claim for the dosage form or a claim for the use of the ingredient.[290] The Canadian PM(NOC) Regulations do not permit listing of process patents on the Patent Register; it remains open for reference biologic holders to enforce these patents outside of the patent linkage framework.

If the reference biologic holder decides to challenge the biosimilar applicant's allegations, it has 45 days from the service of the Notice of Allegation to bring a

[287] Pursuant to ss. 3(2) of the *PM(NOC) Regs*, the Therapeutic Products Directorate is required to maintain a register of patents (Patent Register) that have been submitted for addition to the register and certificates of supplementary protection in which any of those patents are set out. These submissions are assessed to determine whether the therapeutic product falls within the scope of the *PM(NOC) Regs* by the Office of Patented Medicines Liason (OPML).
[288] Canadian PM(NOC) Regulations at s. 4(5). Procter & Gamble Pharmaceuticals Canada Inc. v. Canada (Minister of Health) (2003) 33 C.P.R. (4th) 193 (F.C.A.), reversing on this ground (2003), 26 C.P.R. (4th) 180 (F.C.).
[289] Id. at, at s. 4(6).
[290] Id. at, at s. 4(5). Section 4.5.1 of Canada, Guidance Document Patented Medicines (Notice of Compliance) Regulations. May 11, 2018.

PM(NOC) Action.[291] Commencement of the PM(NOC) Action automatically triggers a 24 month stay prohibiting the Minister of Health from issuing a NOC in respect of the biosimilar.

Generic/biosimilar manufacturers have argued that there is no deterrent to a reference brand/biologic holder to commence an action without regard to the strength of their challenge in order to fully capitalize on the 24-month stay. However, the reference biologic holder that commences a PM(NOC) Action is open to significant liability under s. 8 of Canada's PM(NOC) Regulations for any loss suffered by the biosimilar for the period of time during which the issuance of the generic's NOC was on patent hold where the prohibition proceeding is dismissed or withdrawn or discontinued by the reference biologic holder. If the reference biologic holder decides not to challenge the NOA and takes no action within the 45-day period, Health Canada will be free to approve the biosimilar's NSD/SNDS if otherwise compliant.

The implications of this shift from PM(NOC) Application to PM(NOC) Action has not yet been made clear. The first judgement of the Federal Court of Canada arising from a PM(NOC) Action was rendered only on April 16, 2020 in Amgen Inc. v. Pfizer Canada ULC in respect of Pfizer's biosimilar NIVESTYM (filgrastim) making reference to Amgen's NEUPOGEN (filgrastim). [292] Further, the academic literature is sparse. The legal commentary from the private practice community reiterates the Canadian government's rationale to strike a balance by mirroring traditional patent litigation to achieve the objectives of providing a route of appeal, eliminating dual litigation, enabling parties to advance a full record based on discovery and viva voce evidence. In relying on experience, the advantages of the shift from an application regime to an action regime is significant, but not for reasons related to the stated objectives. As parsed in Chapter 5, framing Canada's patent linkage regime as *in rem* actions allows for

[291] PM(NOC) Regulations at S. 6(1)
[292] 2020 FC 522.

and makes more attractive private settlement agreements between parties that can serve to delay the market launch of biosimilars.

4.2.2. US Biosimilars Act's Patent Linkages – Hatch-Waxman Without The Orange Book

As well as creating an abbreviated pathway for biosimilars, the US' adoption of the US Biosimilars Act shaped a "patent dance" to which all biologic and biosimilar manufacturers are bound to step, linking a biologic's patent right entitlements to the regulatory market authorization of a biosimilar (the "patent dance").[293] However, consideration was not fully given to the various contentious fora – dance floors, to keep the analogy alive – available to these parties. In addition to the traditional court-based litigation contemplated in the patent linkage regime created by §351(l) of the US Biosimilars Act, biologic and biosimilar manufactures may also do battle before the USTPO via patent reissuance reviews and *inter partes* review mechanisms. These proceedings are not directly linked to the regulation of biosimilars, but may be used indirectly to narrow the field of patents that may be asserted by the reference biologic holder when patent litigation comes due. All avenues of patent challenges, linked or otherwise, are addressed in this section.

To put the US Biosimilars Act's patent dance into appropriate context, some consideration must be given to what came before: the *Hatch-Waxman Act* and the "Orange Book Proceedings".[294] Arising from the pharmaceutical experience, the regime created in 1984 by the *Hatch-Waxman Act* linked the approval of generic pharmaceuticals to the patent status of the already approved brand pharmaceutical's product, similar to Canada's PM(NOC) proceedings created in the early 90s.[295] The US Federal Circuit recognized that the *Hatch-Waxman Act* reflects a balance struck by

[293] Lindsay Kelly, *Biologics in the Practice of Law*, 39 HARVARD JOURNAL OF LAW & PUBLIC POLICY 21(2016). Decaire, et al., UNIVERSITY OF SAN FRANCISCO LAW REVIEW, (2012).
[294] Montgomery, UNIVERSITY OF PITTSBURGH LAW REVIEW, (2015).
[295] Kretzschmar, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, 299 (2014).

Congress "between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market."[296]

Like Canada's PM(NOC) Regulations., the *Hatch-Waxman Act* allows generics to submit abbreviated drug submissions comparing its generic drug to the previously approved brand drug and, unlike the biologic/biosimilar paradigm, not have to produce any pre-clinical or clinical data, instead relying on the brand's data. In "exchange" for access to the abbreviated process and reliance on the brand's data, the generic must address all of the brand's patents.

Like the PM(NOC) Regulations And the Canadian Patent Register, the *Hatch-Waxman Act* required the publication of the Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book", lists among other important information, the brand pharmaceutical's patents. During the regulatory assessment process, the brand manufacturers may make an election to include a patent or list of patents to be listed in the Orange Book against the brand pharmaceutical ensuring that if a generic were to reference that particular brand, the generic manufacturer would have to address each listed patent – usually alleging either non-infringement or invalidity – or wait until the expiry of each and every patent before the generic's launch if approved by the US FDA. Listed patents may only include patents related to the active ingredient, product and approved uses of the product.

The US Biosimilars Act does not mandate a list of biologic products similar to the Orange Book; however, the US FDA has taken the initiative to create an analogous reference guide formally known as the Lists of Licensed Biological Products with Reference Products Exclusivity and Biosimilarity or Interchangeability Evaluations, commonly known as the Purple Book. While not applicable to biologics and biosimilars, the *Hatch-Waxman Act* and Orange Book share some broad stroke foundational principles and

[296] *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). See also id. at, 298.

similarities with the patent linkage regime created by the US Biosimilars Act. Like the Orange Book, the Purple Book is a list of all biologics and biosimilars granted market authorization pursuant to §351(a) (biologics) and §351(k) (biosimilars) of the US Public Health Services Act,[297] respectively. A marked and *significantly deficient* departure from the Orange Book (and the Canadian Patent List) is the lack of patent listed in the Purple Book.

Some interesting characteristics of the patent dance created by §351(l) codified in the US Public Health Services Act become apparent upon closer examination and as a consequence of this key distinction.[298] But prior to this analysis, the full patent dance process is set out in the following table:

TABLE 5 – STEPS IN THE US BIOSIMILARS ACT PATENT DANCE[299]

Elapsed Time	Step
Step 1 – Information Exchange	
+20 days	Within 20 days of FDA's notification that the biosimilar license application has been accepted, biosimilar applicant sends a notice of filing (BLA Filing Notification) and copy of the biosimilar license application to the reference biologic holder as well as manufacturing information pertinent to the BIOSIMILAR LICENSE APPLICATION, and may provide additional information as requested by reference biologic holder. This information may be provided under statutory and/or contractual confidentiality terms.
+80 days	Within 60 days of the BLA Filing Notification, reference biologic holder provides the biosimilar applicant with a list of patents* for which it could bring a claim of patent infringement and a list of patents it is willing to license to the applicant
+140 days	Within 60 days of receiving the Biologics Patent List, the biosimilar applicant provides: (1) a list of patents that it believes the reference biologic holder could bring a claim of infringement in respect of and (2) detailed statements why, claim-by-claim, each patent is invalid, unenforceable, or not infringed by the biosimilar applicant; (3) may include a statement when the biosimilar applicant intends to launch its biosimilar, potentially after the expiry of one or more patent and (4) whether it would consider a license to one or more patents listed in the Biologics Patent List
+200 days	reference biologic holder provides: (1) a claim-by-claim of why it believe each Biologics Patent List patent is valid, enforceable and infringed by the biosimilar applicant.
After Above:	For 15 days of good-faith negotiations, the biosimilar applicant and reference biologic

[297] Not currently indicated on the Purple Book is the biosimilar approval basis – biosimilarity vs. interchangeability – which will likely be required once the Purple Book becomes statutorily mandated.
[298] Dougherty, FOOD & DRUG L.J., (2010).
[299] Summary compiled from the relevant statutory provisions in the US Biosimilars Act, in addition to other sources such as id. at. and Brian J. Malkin, *Biosimilars patent litigation in the EU and the US: a comparative strategic overview*, 4 GENERICS AND BIOSIMILARS INITIATIVE JOURNAL 113(2015).

+15 days	holder attempt to agree on a list of patent to litigation prior to product launch as an "artificial" act of infringement given that there will be no actual infringement until the product is marketed, but the litigation is predicated on the biosimilar's assertion that it intends to market its biosimilar, if approved, prior to the expiry of one or more of reference biologic holder's patents.
	If negotiations fail, the biosimilar applicant and reference biologic holder compile their own lists as follows:
	biosimilar applicant provides a list of patents to be litigated
+20 days	Within 5 days of receipt of biosimilar applicant's Litigation Patent List, reference biologic holder provide a list of patent that may not exceed the number of patents on the biosimilar's Litigation Patent List. Where the biosimilar Asserted Patents List contains no patents, reference biologic holder may include one patent in the Litigation Patent List.
+50 days	Within 30 days, reference biologic holder must commence an action against the biosimilar applicant ("timely infringement suit"). RPB holder is limited to only royalty recovery (not damages or injunctive relief) where: (1) reference biologic holder fails to bring a timely infringement suit or (2) the action is dismissed without prejudice or not prosecuted to judgment in good faith.
Step 2 – Market Launch Notification	
- 180 days	biosimilar must provide 180 day advance notice prior to commercial launch, thereby allowing for the following actions to be taken in respect of the patent lists (as modified by newly issued or licensed patent):
	reference biologic holder or biosimilar applicant can seek a declaratory judgement; and
	reference biologic holder can seek a preliminary injunction before the intended date of first market launch.

*Newly issued or licensed patents must be added to the patent lists within 30 days of issuance or licensing.

The implications of the patent dance are not necessarily evidence on the face of the process as set out above; however, the practical implications, in light of recent case law, has significant influence on the conduct of biosimilar applicants and reference biologic holders as they attempt to navigate the strange pre-litigation steps that, in some respects, require engagement of the parties prior to the commencement of litigation. Specifically, there are five consequences arising from the patent dance and its recent judicial consideration that warrant some commentary.

First, the lack of patent list on the Purple List means that a prospective biosimilar manufacturer is precluded from the benefit of having a relatively known universe of patents disclosed well in advance; the ability to make commercial and R&D decisions in light of the patent landscape for a particular target is significantly curtailed and only

mitigated by expensive, lengthy and qualified freedom to operate opinions. This deficiency in transparency has been widely and justifiably criticized by Jeffery Wu and others.[300] This situation is exacerbated by the increasing prevalence of the patent thickets introduced in Chapter 2 related to a given biologic that may be asserted against the biosimilar, but there is no certainty of what patents may be put into play either way until the biosimilar is developed and advances through the market approval process – i.e., after the significant investment of money and years later. Contradictorily, patent counsel with the biologics industry group BIO has recently taken the position that even if patent information was forced to be disclosed for the sake of transparency, transparency will not be achieved because "[w]e're going to end up with very large lists of patents that people will not understand.… I don't think this is going to create a lot of transparency," while at the same time asserting that patent thickets are not an issue even though he states that "a lot of patents, frankly, that aren't specific to the biosimilar products but that relate more generally to recent modern methods of biologics manufacturing."[301]

Second, the US Biosimilars Act created two phases in the patent linkage litigation scheme, the first setting out default obligations for the exchange of information that have since been held to be voluntary. The biosimilar applicant is required to voluntarily disclose its biosimilar license application and process of manufacture information, as well as identify the patents it thinks are applicable to the reference biologic holder's patents(s) that may be asserted against the proposed biosimilar applicant's application.

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[300] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019). See also Mehr, (2020). Jonathan Stroud, *THE ILLUSION OF INTERCHANGEABILITY: THE BENEFITS AND DANGERS OF GUIDANCE-PLUS RULEMAKING IN THE FDA'S BIOSIMILAR APPROVAL PROCESS*, 63 ADMINISTRATIVE LAW REVIEW (2011). Kelly Davio, *Congress Votes on Amending Orange and Purple Books in Effort to Encourage Generics and Biosimilars* (May 8, 2019), *available at* https://www.centerforbiosimilars.com/news/congress-to-vote-on-amending-orange-and-purple-books-in-effort-to-encourage-generics-and-biosimilars. Kate Cook, *How The Purple Book Continuity Act Could Challenge Biosimilars & The FDA* (May 7, 2019), *available at* https://www.biosimilardevelopment.com/doc/how-the-purple-book-continuity-act-could-challenge-biosimilars-the-fda-0001. <*New Biologics Pathway Could Be Daunting for Biologics Developers.pdf*>;Davio. May 8, 2019;Cook. May 7, 2019;Stroud, ADMINISTRATIVE LAW REVIEW, (2011).

[301] Tony Hagen, *Patent Thickets Are Not the Obstacle They Appear to Be, BIO Patent Counsel Claims* (March 14, 2020), *available at* https://www.centerforbiosimilars.com/news/patent-thickets-are-not-the-obstacle-they-appear-to-be-bio-patent-counsel-claims.

As established below, biosimilar applicants are not willing to do so, and reference biologic holders are limited to the remedies in the US Biosimilars Act which does not include injunctive relief.

Third, the US Biosimilars Act dictates ramification where parties do not engage in voluntary exchanges including limited litigation rights; injunctive relief has been held to be outside of the scope of the US Biosimilars Act's patent linkage regime by the US Supreme Court.[302]

Fourth, (absent the application of the US Supreme Court's *ratio* in Amgen v. Sandoz discussed below), the cumulative effect of multiple tightly sequenced steps that the parties are obliged to take, hence the common moniker "patent dance", results in an overall lengthy period before any patent infringement action could be brought. Critically, this could potentially be after the FDA accepts the biosimilar application for filing and begins its assessment.

Five, following the initial exchange of patent lists, the multiple short time-framed steps are in fact substantive patent litigation steps required to be taken between 180 days prior to the biosimilar's commercial launch and post launch. These steps involve complicated patent assessment, analysis and responses on very tight deadlines with the potential for significant consequences.

In 2017, the US Supreme Court issued its first and, thus far, only decision relating to biosimilars and the US Biosimilars Act's patent dance.[303] In the 9-0 ruling, the Court held that biosimilar applicants are not required to share their biosimilar license application information with the reference biologic holder. Further, the biosimilar applicant's 180 day intention to launch the biosimilar on the market, namely Step 2, could be served prior to receiving the FDA's approval of the biosimilar. Given its implications, and as a

[302] Sandoz v Amgen, 137 S. Ct. 1664 (2017).
[303] Sandoz v Amgen, 137 S. Ct. 1664 (2017)

potential basis for further legislative reform, this decision warrants further consideration. Ultimately, it was hailed as a victory for the biosimilars industry.[304]

Sandoz, the biosimilar applicant, submitted an abbreviated biosimilar license application for ZARXIO® (filgraztim-sndz), making reference to the reference biologic NEUPOGEN® (filgrastim) produced by Amgen, the reference biologic holder.

As set out in detail in Table 5, Step 1 of the patent dance is to facilitate the exchange of information related to the biosimilar's abbreviated license application, its manufacturing process and the reference biologic holder's patents, all of which is confidential and/or commercially sensitive information. The provision of biosimilar applicant's information is to allow for the reference biologic holder to assess potential patent infringement claims. Step 2 is the market launch notification; the biosimilar applicant shall provide notice of its intention to enter the market no later than 180 days before launching the biosimilar on the market.

In the case before the US Supreme Court, Sandoz (biosimilar) did not comply with Step 1 purporting to protect its complex manufacturing processes and intellectual property. Amgen (reference biologic) unsuccessfully sought an injunction in the Federal Circuit to force the disclosure of Sandoz' (biosimilar) information.

In respect of Step 2, Sandoz (biosimilar) served its Market Launch Notice to Amgen (reference biologic) before receiving FDA approval of its biosimilar. Amgen (reference biologic) took the position that the Market Launch Notification could only be granted after FDA approval, not in advance.

The US Supreme Court sided with Sandoz (biosimilar) on both counts. In respect of Sandoz' non-compliance with Step 1, the trial court and Federal Circuit held that injunctive relief was not statutorily available as a remedy for Sandoz' (biosimilar) lack of disclosure. However, the Federal Circuit did agree with Amgen's (reference biologic)

[304] Ameet Sarpatwari, et al., *The Supreme Court Ruling in Sandoz v Amgen: A Victory for Follow-on Biologics*, 178 JAMA INTERNAL MEDICINE (2018).

position that the Market Launch Notice should only come from Sandoz (biosimilar) after it received FDA approval for its biosimilar.

In relying on strict statutory interpretation, the US Supreme Court reversed the Federal Circuit's decision in respect of Step 2 finding that the language mandating the Market Launch Notice, without further condition or requirement, was intentional. Other time limits in the US Biosimilars Act were made conditional or contingent, but no such restriction was imposed on the Market Launch Notification by Congress.

More significantly, however, the US Supreme Court held that no injunctive relief was available to Amgen (reference biologic) to redress Sandoz' (biosimilar) failure to comply with the information disclosure obligations in Step 1. The US Biosimilars Act, as written, was held to already provide a remedy, namely the ability to litigate the question of patent infringement before the biosimilar's launch; it would be inappropriate to read into the legislation an additional injunctive remedy that was non-existent.

Amgen's (reference biologic) injunctive relief argument may not be entirely dead since this argument was also pursued under California's unfair competition statue, an argument that the US Supreme Court remanded back to the Federal Circuit for determination. On remand, the Federal Circuit held that the US Biosimilars Act supersedes Amgen's (reference biologic) state-law based claims.

The practical effect of the US Supreme Court's ruling is that it gives biosimilar applicants more control over the strategic timing of the Market Launch Notification which is in essence the trigger for litigation associated with the biosimilar and reduces the reference biologic holder's market exclusivity without having to engage in patent litigation to as little as 6 months, depending on the FDA's approval processing times among other factors.

In addition to the direct impact that patents have in terms of the US Biosimilars Act patent linkages, there is also an avenue to effect indirect changes to a reference biologic

holder's patent portfolio in advance of becoming a bar to a biosimilar through the patent linkage regime. This indirect process, namely *inter partes* review (IPR),[305] was created by the America Invents Act in 2011 where questions of patent validity, (specifically anticipation[306] and obviousness[307]) may be raised shortly after patent issuance, but where no declaratory action has been filed.[308]

Inter partes review proceedings is fertile ground for much examination and debate, but the primary relevance of *inter partes* reviews to the research at hand is the way in which the *inter partes* review process provides an option, albeit potentially difficult,[309] that may affect the number of patents that ultimately may be asserted against the biosimilar applicant through the patent dance, or those that may be asserted through traditional patent litigation outside of the US Biosimilars Act patent linkages.[310]

Prior to the creation of *inter partes* review proceedings, questions of validity were primarily dealt with before the federal district courts which are long, involved and expensive proceedings.[311] The impetus for their creation was to provide a quicker and less expensive way to an answer on the validity of a patent. However, *inter partes* review proceedings are a double edge sword. On one hand the benefits of *inter partes* review proceedings to biosimilar challengers are: (1) the presumption of validity does not apply (2) the legal burden is to establish grounds of invalidity on the preponderance of the evidence and (3) adjudication is by a technically trained administrative patent judge within the Patent Trial and Appeal Board (PTAB) at the US Patent and Trademarks Office (USPTO) and (4) set proceedings timeframe of 24 months. However, where *inter partes* reviews are brought and the validity of the patent is upheld, estopple precludes

[305] The America Invents Act also created the post grant review process, but it is applicable to patents with a priority date later than March 15, 2013. Thus the majority of challenges to biologic patents proceed by way of *inter partes* review.
[306] 35 USC §102
[307] 35 USC §103
[308] Malkin, GENERICS AND BIOSIMILARS INITIATIVE JOURNAL, (2015).
[309] Wu & Cheng, CHI.-KENT J. INTELL. PROP., 147 (2019).
[310] Decaire, et al., UNIVERSITY OF SAN FRANCISCO LAW REVIEW, 1062-3 (2012).
[311] Id. at.

the biosimilar challenger from subsequently challenging the validity of the patent on any ground that were or reasonably could have been brought in the *inter partes* review proceeding thereby limiting the defense possibility in the instance the biosimilar is sued for infringement either within the context of the US Biosimilars Act patent linkage proceeding or separately through traditional patent litigation.[312]

The constitutionality of the *inter partes* review procedure was discussed and debated in the literature[313] and in the Courts prior to the US Supreme Court's decision in *Oil States v. Green Energy Group*.[314] The question before the Court was whether the *inter partes* review procedure was an unconstitutional "taking" of property rights by the government without a jury trial. As a "public franchise" rather than a private "property right", the Court held that a government agency can make determinations on the validity regarding government granted patent rights without a jury trial. The result is that biosimilars manufacturers can seek to clear the patent thicket at any time and outside of the patent dance. This position makes sense; the PTAB can address questions of anticipation and obviousness in a more timely and cost-effective forum to adjudicate whether or not there was even the existence or entitlement to a right which is not a determination of whether the right was taken away.

4.2.3. No EU Community Patent Linkages

Community ties bind the EU and EEA member states together both economically and legally, but there remains a great deal of national juridical independence in respect of intellectual property laws, among other areas. As a result, the EU's approach to patent

[312] Malkin, GENERICS AND BIOSIMILARS INITIATIVE JOURNAL, (2015).
[313] Erika Lietzan & Julia Post, *The Law of 180-Day Exclusivity*, 71 FOOD AND DRUG LAW JOURNAL (2016). See cited references Jaimin Shah, Comment, *Pulling the "Trigger" on the Hatch–Waxman Act's 180–Day Exclusivity Using Inter Partes Review*, 14 J. MARSHALL REV. INTELL. PROP. L. 453 (2015) (arguing that a final inter partes review decision should qualify as a policy matter); Brian T. Apel, Note, *An Administrative Meter Maid: Using Inter Partes Review and Post– Grant Review to Curb Exclusivity Parking Via the "Failure to Market" Provision of the Hatch–Waxman Act*, 114 MICH. L. REV. 106, 107 (2015) (concluding that inter partes review is unlikely to qualify).
[314] Oil States v. Green Energy, 584 U. S. __ (2018). Chen, et al., DRUGS, (2018).

linkages is entirely dissimilar to the US and Canadian approach – they are effectively non-existent. The EU has taken the position that patent linkage is contrary to the EU's early working exception afforded to generic pharmaceuticals, and now biosimilars. Specifically, patent linkages are considered unlawful under Regulation (EC) No 726/2004 and Directive (EC) No 2001/83.[315] In direct contrast with the US and Canada, the status of a patent is not a ground for the refusal or delay of approval for a biosimilar in the EU. Attempts to introduce patent linkages has been made by brand industry lobbying,[316] and indeed patent linkages or national laws that deter the approval and adoption of generics still exist today in the EU. However, the EU Commission has previously taken action indicating that patent linkages are not supported and are expressly opposed at the member state level.[317]

While there is a high degree of integration in the prosecution of patents before the EPO, the assertion and enforcement of granted patents must be brought before domestic courts where inherent jurisdictional challenges abound.[318] Domestic patent litigation strategy between biologic and biosimilar manufacturers has become a tactical game that relies and plays-off against the various predilections of each member state.[319] However, these patent challenges are, at least in the more significant states in the EU economic community,[320] uncoupled from the EMA's assessment of a given biosimilar referencing a biologic.

Accordingly, most patent-based challenges in the EU are founded in the opposition mechanism available to third-parties before the EPO. The EPO has 38 contracting states and provides unified patent prosecution and opposition mechanisms with the option to obtain national patents at the election of the patent applicant after prosecution.

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[315] European Commission, *Pharmaceutical Sector Inquiry – Preliminary Report Fact Sheet "Regulatory Framework"*.
[316] And again in 2014 by the European Federation of Pharmaceutical Industries and Associations (EFPIA).
[317] EU formally requested Italy to drop its linkage requirements in 2012.
[318] Unified Patent Court note
[319] Malkin, GENERICS AND BIOSIMILARS INITIATIVE JOURNAL, 114 (2015).
[320] Some states do have some form of patent linkages, but these are not connected with the EMA's assessment.

Oppositions may be filed by any public member(s) within 9 months of patent grant, public notice provided.

This approach enables a biosimilar manufacturer to challenge a reference biologic holder's key patents in a single forum rather than multiple state patent courts. For example, oppositions were filed for epoetin (Amgen's reference biologic EPOGEN (epoetin)), filgrastim (Amgen's reference biologic NEUPOGEN (filgrastim)), infliximab (Janssen's reference biologic REMICADE (infliximab)), insulin glargine (Sanofi's reference biologic LANTUS (insulin glargine)), and somatropin (Pfizer's reference biologic GENOTROPIN (somatropin)).[321]

There are, however, disadvantages in proceeding by way of opposition before the EPO; the few limited grounds to revoke a patent available during opposition proceedings focus on whether there was a defect in the assessment leading to the grant of the patent. These grounds include (1) the subject matter is not patentable; (2) the invention was not disclosed clearly or completely enough for one skilled in the art to perform the invention; or (3) the subject matter extends beyond the content of the application filed.[322] Thus, the mainstream issue of patent infringement usually at play in traditional patent litigation plays no role before the EPO.

There are three main outcomes of opposition proceedings: (1) the opposition is rejected and the patent is maintained as granted; (2) the patent is maintained in amended form with a new published specification; or (3) the patent is revoked. Initial opposition decisions may be appealed within two months; countries may have conflicting rules whether they stay any national patent infringement actions while an opposition and any associated appeal is pending.[323] The median time for an appeal is close to three years, which is the same approximate median time for an opposition for pharmaceutical/biologics patents.

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[321] Malkin, GENERICS AND BIOSIMILARS INITIATIVE JOURNAL, 114 (2015).
[322] Id. at.
[323] Id. at.

The commencement of opposition proceedings (by the biosimilar applicant) does not preclude the commencement of domestic patent litigation by either party; the reference biologic manufacture may seek redress for patent infringement while the biosimilar applicant can seek declarations of patent invalidity. Unfortunately, pursuing patent litigation strategies in different jurisdictions will require expertise of local practice and specialized patent counsel – a vastly expensive and resource intensive proposition.

Regardless of the perpetrating party, biologic/biosimilar patent litigation in the EU is messy; multijurisdictional litigation strategy appears chaotic, but does make for profoundly fertile ground for further research and industry insight as the area evolves.

The crux of the matter, however, is that there is no linkage between EMA/CHMP's regulatory assessment and any patent consideration, save for the tangential connection resulting in coterminous exclusivity and patent expiry. However, this begs the question of "why didn't the EU adopt a patent linkage regime?"

4.3. Data Exclusivity Provisions in Canada, the US and EU

Data exclusivity was first introduced in the US in 1984 with the *Hatch-Waxman Act* and has since permeated throughout the world, as detailed in Chapter 3, through international trade agendas and their accompanying treaty obligations prompted by the US, EU and their pharmaceutical industries. During the negotiation of this legislation, brand pharmaceutical companies advocated for additional protection against generics in order to preserve the incentive for continued innovation with greater certainty of their return on investments commensurate with the risk.[324]

Biosimilar manufacturers are not precluded from generating their own clinical efficacy data to circumvent data exclusivity, but this is a costly approach and potentially creates some serious ethical issues. That is, some clinical trial participants would not receive

[324] Ohly & Patel, JOURNAL OF INTELLECTUAL PROPERTY LAW & PRACTICE, 476-477 (2011).

treatment (the biologic) that has already been shown to be safe and effective in order for data on the biosimilar to be garnered. Further, clinical trial participants would also be taking the risk of taking a drug where the knowledge and information about the drug already exists. The reality is that while biosimilar manufacturers may be required to carry out non-clinical and clinical trials, these trials are not identical to the clinical trial upon which basis the biologic was granted approval and, more importantly, the data to which the biosimilar applications rely upon through the abbreviated pathway created by the US Biosimilars Act.[325]

Generally, data exclusivity provisions protect the data of a biologics manufacturer who submits the first application for a biologic from allowing a biosimilar applicant to rely on the biologic's data for comparison purposes during the biosimilar regulatory assessment. Legislation in many countries, including Canada, the US and EU, allow a biosimilar applicant to make reference and rely upon comparisons to the data and evidence of a previously approved reference biologic.

This ability for the biosimilar to rely upon the reference biologic data represents a significant savings in costs and resources that would otherwise have to be expended on expensive testing and clinical trials establishing the safety and efficacy of the biosimilar. Instead, the biosimilar applicant benefits from the reference biologic holder's efforts by having to establish the safety, effectiveness and potency in relation to the reference biologic. While in comparison to the costs and resources expended by the reference biologic manufacturer, the biosimilar manufacturer's comparative submission is less expensive and onerous to produce, it is by no means without considerable cost and effort.

It is therefore a policy objective of data exclusivity provisions to provide reference biologic manufacturers with time to recover the substantial investment and costs

[325] Id. at, 471.

incurred in the R&D and commercialization of the biologic, through market exclusivity, before the competitive biosimilar entry into the marketplace.

As detailed below, data exclusivity as solely a bar to market entry has evolved; it protects the disclosure and the use of the reference biologic holder's data which, in practice, has created two types of prohibitions. First, the prohibition for a period of time that precludes the biosimilar from entry into the market after approved ("Market Entry Prohibition Period"). Second, is the prohibition for a period of time that preclude a biosimilar application, relying on an reference biologic, from being either assessed or even accepted for filing with the regulator ("filing prohibition period").

The rationale for the filing prohibition period is that the biosimilar should not enjoy the springboard benefit of relying on the reference biologic, namely using the Market Entry Prohibition term for the biosimilar to be assessed and granted market authorization such that it is ready for launch immediately after the expiry of the Market Entry Prohibition. The filing prohibition period is thought to equalize the prejudice caused by the lengthy regulatory approval process.

It should be noted that data exclusivity provisions are independent of the patent protection realities that will continue to be the focus of biologic companies' strategy to protect market exclusivity. Separate and apart from the status of patents relating to the biologic, a biosimilar applicant will be precluded from relying on the reference biologic holder's data for the purposes of obtaining regulatory authorization until after the various periods of data exclusivity have expired. However, the potential and future power of these regimes cannot be discounted; data exclusivity creates strong monopolies that are automatically granted and enforced without significant contest by regulatory agencies, without limited exceptions or conditions.

4.3.1. Data Exclusivity in Canada

Amendments to the Canadian *FDA Regs.* enacted on October 5, 2006, implemented Canada's data exclusivity obligations required by TRIPs as a member of the World Trade Organization as well as the North American FTA (1994).[326] Specifically, Canada has an obligation to provide protection to data that is required to be submitted for the purpose of obtaining regulatory approval of pharmaceutical products from disclosure or unfair commercial use.

Canada's data exclusivity provisions are intended to provide the manufacturer of an innovative drug with an internationally competitive, guaranteed minimum period of market exclusivity; thus providing an adequate incentive for innovators to invest in research, and to develop and market their products in Canada.[327] As confirmed by caselaw and the purpose statement in section C.08.004.1(2) of the FDA Regs., data exclusivity eligibility has two requirements: (1) it applies only to a new chemical entity, and (2) the production of the supporting data under consideration required considerable effort.[328] Examples of new and significant data requiring considerable effort to generate include clinical trials providing data and evidence to determine the safety, efficacy, properties, and conditions of use of a reference biologic. However, data and evidence submitted from secondary sources such as literature references and/or post-market domestic or foreign experience would not be considered data eligible for protection. [329] Data exclusivity has a tumultuous history in Canada despite its longstanding presence in our legislation. Prior to 2006, the prior version of C.08.004.1 of the *FDA Regs.*, purported to provide 5 years of data exclusivity, was narrowly interpreted by the Federal Court of Appeal rendering the provision rarely triggered.[330]

[326] Regulations Amending the Food and Drug Regulations (Data Protection), SOR/2006-241.
[327] Government of Canada, Guidance Document Data Protection under C.08.004.1 of the Food and Drug Regulations (Health Canada ed., May 16, 2017).
[328] Id. at, 3.
[329] Id. at, 6.
[330] Bayer Inc. v. Canada (Attorney General) (1998) 84 CPR (3d) 129 (FCTD), aff'd (1999) 897 CPR (3d) 293 (FCTD), leave to appeal refused (2000), 5 CPR (4th) vii (SCC).

The pre-October 2006 data exclusivity states that if the Minister of Health, in support of a manufacturer's drug submission: (1) "examines any information"; and (2) "relies on data" contained in the information or material filed by the brand pharmaceutical and for which a Notice of Compliance has already issued, a Notice of Compliance shall not be issued to the subsequent-entry manufacturer earlier than 5 years after the date of issuance of the brand's Notice of Compliance.[331] In *Bayer*, the Federal Court of Appeal decision interpreted this provision narrowly to require that the Minister actually examine and rely on the brand's data in considering an abbreviated drug submission and the bioequivalence of the generic drug. An actual examination of the brand's data and information was rarely done or relied upon, therefore there was no effective data exclusivity protection in Canada prior to October 2006.

As a result from mounting pressure from the US and its pharmaceutical lobby, the state of affairs in Canada changed in 2006. The Regulatory Impact Analysis Statement ("RIAS") accompanying the October 2006 amendments acknowledged that the Minister did not in the ordinary course actually examine the innovative drug submission despite the reliance on that submission in assessing the bioequivalence of a subsequent-entry drug. Accordingly, the RIAS explains that the amendments serve to re-characterizes the triggering of the post-October 2006 data protection provisions "to clarify that the aforementioned reliance will give rise to an exclusionary period."[332] However, this amendment went beyond providing clarity. Unsurprisingly, given the political climate and the spread of TRIPs-plus provisions due to the advancement of bilateral and multilateral trade agreements, brand companies took the position that Canada should be adopting a data protection period consistent with the EU. Further, the brand industry advocated for an expansion of the applicability of data exclusivity on a variety of grounds, but most notably an expansion beyond the definition of "innovative drug" to include all products containing the medicinal ingredient like combination products and

[331] C.08.004.1 of the *Food and Drug Regulations*

[332] Regulations Amending the Food and Drug Regulations (Data Protection) SOR/2006-241, Regulatory Impact Analysis Statement, Canada Gazette Part II, Vol. 140, No. 21, October 18, 2006, p. 1495-1502 at •.

different formulations and polymorphs.[333] Proponents of the generic industry asserted, among other things, that the pre-2006 data exclusivity approach endorsed by Bayer was in keeping with Canada's obligations and should not be disturbed. Any implementation of a filing prohibition or authorization prohibition as published for comment went beyond the scope of Canada's international obligations. This is a position with which I am inclined to agree. Canada unilaterally, even if under pressure, amended its data exclusivity obligations to mirror the regime in the US and EU.

Section C.08.004.1(1) defines "innovative drug" as "a drug that contains a medicinal ingredient not previously approved in a drug by the Minister and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate or polymorph."[334] In the context of interpreting the term "innovative drug", the Federal Court of Canada recently rendered a decision in respect of Canada's data exclusivity provisions and acknowledging the necessity of considering the context of Canada's international obligations. The Courts have previously acknowledged that there is a difference between Canada's international obligations and the way in which these obligations are nationally implemented. The obligations arising from the North America FTA (1994) and TRIPs are to protect data from disclosure or unfair commercial use. How Canada chose to meet this obligation is by conferring data exclusivity pursuant to C.08.004.1(3) making the "innovative drug" the "vehicle" through which its data may be protected in the event of a comparison to the "innovative drug".[335] The Court considered the context of Canada's international obligations relevant to, though not determinative of, the interpretation of its current data exclusivity provisions.[336]

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[333] Regulatory Impact Analysis Statement, Canada Gazette Part II, Vol. 140, No. 21, October 18, 2006, p. 1495 at 1501-2.

[334] FD Regs. CRC c. 870, s. C.08.004.1(1) at am. By SOR/2006-241. By its very definition, "innovative drug" is not a "salt, ester, enantionmer, solvate or polymorph", but the jury is still out on whether the data supporting an NOC for a pro-drug or metabolite of a previously approved drug would be eligible for data protection.

[335] Apotex at paras 76, 85–88.

[336] Natco Pharma (Canada) Inc. v. Canada (Health), 2020 FC 788 at para. 15-17 relying on Teva at paras 35–39; Apotex at paras 75–77, 90–91; Takeda at paras 129–131

Thus, the decision of how Canada implemented its perceived obligations pursuant to the North America FTA (1994) and TRIPs was Canada's own doing, but the subsequent interpretation of its national provision will be undertaken in light of the intent of its international obligations which have been found to be consistent with existing case law taking the rational approach of limiting the applicability of data exclusivity to "innovative drugs" as "new chemical entities".[337] Under the current data exclusivity provision, Canada provides for an 8 year approval prohibition period from the date the first NOC was issued to the biologic "innovative drug" reference product comprising the identical medicinal ingredient precluding the approval of a biosimilar. Where there are paediatric studies have been submitted within the first 5 years of the issuance of the innovative drug's NOC, the 8 year period will be extended by 6 months. Approval for a biosimilar in Canada proceeds by way of a new drug submission, but nonetheless seeks to reduce the clinical and non-clinical study requirements by demonstrating similarity to a previously approved reference biologic drug. Accordingly, a biosimilar will not be considered to be an "innovative drug". As well, the current provision establishes a 6 year filing prohibition period of an biosimilar application from the date of issuance of the first NOC for the biologic "innovative drug".

While C.08.004.1(5) excludes a biologic from data exclusivity where the reference biologic is not marketed in Canada, the application of this exclusion might be ambiguous. This exclusion to data exclusivity applies where the drug identification number (DIN) for the reference biologic was cancelled or the reference biologic was otherwise withdrawn from the market. However, the enforceability of data exclusivity might be called into question where the reference biologic has been issued an NOC, but has not been marketed in Canada after authorization has been granted.

[337] See Epicept Corporation v Canada (Health), 2010 FC 956 at paras 62, 65, 78, Teva Canada Limited v Canada (Health), 2012 FCA 106 at para 42, Celgene v Canada, 2013 FCA 43 at paras 41–46, Takeda Canada Inc v Canada (Health), 2013 FCA 13 at paras 122–131.

4.3.2. US Data Exclusivity

The US Biosimilars Act prohibits the filing of a biosimilar application pursuant to §351(k) until at least 4 years after the date the FDA first approves the reference biologic, i.e., a 4-year filing prohibition period.[338] However, it is the prohibition for the licensing of a biosimilar for the very significant period from the date of the first license grant of the reference biologic that astonishes, namely a 12 year approval prohibition period.[339] This 12 year approval prohibition is over double the period that is mandated by the *Hatch-Waxman Act* for pharmaceuticals, a 5-year approval prohibition period. It is important to also note that a 3-year authorization prohibition for previously approved pharmaceutical where the new or supplemental drug application is based on a new clinical investigation, e.g., a new indication for an existing pharmaceutical.[340] No such exclusivity expanded scope of protection for biologics exist.

As well, the US Biosimilars Act extends the data exclusivity periods an additional 6 months where the reference biologic license applicant includes or is requested by the FDA to include paediatric studies such that it will be 12-½ years before the biosimilar can gain market access and 4-½ years before the FDA will accept the filing of an application for a biosimilar.[341]

Much commentary has been devoted to the implications of the US' biologics data exclusivity regime. Erika Lietzan, previously a brand pharmaceutical litigator, argues that data exclusivity is a myth that has been created to reframe the concept of ownership over data generated for the purpose of regulatory assessment and approval. In essence, she argues that a reference brand/biologic holder's data may be indefinitely protected and ownership continuously maintained, but for being compelled to disclose same in the course of seeking market authorization. In this way, market exclusivity is a fiction

[338] US Public Health Services Act at §351(k)(7)(b)
[339] US Public Health Services Act at §351(k)(7)(a). Montgomery, UNIVERSITY OF PITTSBURGH LAW REVIEW, (2015).
[340] 42 USC §262(7)
[341] US Public Health Services Act at §351(m)(2)(a)

since the government cannot give to the brand something that the brand already owns. Thus, the 12-year market exclusivity is an unreasonable and unjustified truncation of perpetual data exclusivity.[342] However, a helpful review of the justifications for the 12 year exclusivity period, including their underlying assumptions, provided by Julie Polovina cast this extended duration into doubt.[343]

During the negotiation of the US Biosimilars Act, various stakeholders proposed a range of exclusivity terms and put forth studies analyzing the length of time it took a reference biologic holder make back the initial research and development investment. Renowned academic Henry Grabowski submitted report indicating that it took 12.9 to 16.2 years after a reference biologic holder received FDA approval to recover these costs.[344] The biologics industry group BIO advocated for a 14-year exclusivity period as an "insurance policy" for situations where a biosimilar applicant was able to "work around" the reference biologic holder's patents.[345] Notably, there was no mention of the lawful entitlement to do so or even scenarios considering the invalidity of said patents. In 2009 the Federal Trade Commission (FTC) reported that a 12 to 14 year exclusivity period was unnecessary to encourage innovation.[346] Based on updated research from Prasad and Wouters,[347] we now know that the profitability underlying such an extended 12 year exclusivity period is unjustified.

The US Biosimilars Act also awards limited data exclusivity to the first market authorized biosimilar thereby precluding the market authorization of further biosimilars. The data exclusivity period attributable to the first biosimilar ranges between 12 to 42 months, depending on a variety of factors. Pursuant to §351(k)(6)(a) of the US Patient Health

[342] Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91(2016).
[343] Julie Polovina, *Mutant Biologics: The 2010 Health-Reform Legislation's Potential Impact on Reducing Biologic Research and Development Costs*, 100 GEORGETOWN LAW JOURNAL (2012).
[344] Henry Grabowski, Data Exclusivity for New Biological Entities 2 (June 2007), available at http://public.econ.duke.edu/Papers//PDF/DataExclusivityWorkingPaper.pdf.
[345] BIO, A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES 4 (2007).
[346] Michael S. Wroblewski et al., FTC, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG Competition vii (2009).
[347] See *supra* Section 2.2.

Services Act, the first biosimilar is granted an exclusivity period of one year after the date of market entry after which time any other biosimilar may be granted market authorization by the FDA.[348]Data exclusivity grants to the first biosimilar are significantly impacted where the reference biologic holder and biosimilar applicant engage in patent litigation. A grant of market authorization for a further biosimilar may be delayed by 18-months in the event of a final court decision or dismissal (with or without prejudice) on all patents-in-suit against the first biosimilar.[349] Practically speaking, the reference biologic manufacturer maintains its market exclusivity pending the related patent linkage litigation. Given that the first biosimilar applicant was required to engage in litigation, regardless of the outcome, it is awarded an 18-month period of exclusivity to the exclusion of other biosimilars. If the patent linkage litigation is prolonged for at least 42 months, any other biosimilars must wait 42 months after approval of the first biosimilar.[350]

In the event that the reference biologic manufacturer does not engage the first biosimilar applicant in litigation, any further biosimilar applicants must still wait 18 months after approval of the first biosimilar.[351] Practically, the biologic and first biosimilar manufacturer may enter into a settlement agreement and apportion the statutory exclusivity periods privately between them to the exclusion of further biosimilars. Use of settlement agreements can occur because, unlike the Hatch-Waxman regime for pharmaceuticals, patent litigation is not required under the US Biosimilars Act — instead, negotiation is encouraged. As a result, the innovator manufacturer can avoid litigation and negotiate a settlement with the first biosimilar manufacturer, thereby obtaining an additional 18-month period of marketing exclusivity and potentially benefits from royalty payments once the first biosimilar launches.

[348] US Public Health Services Act at §351(k)(6)(a)
[349] US Public Health Services Act at §351(k)(6)(b)
[350] US Public Health Services Act at §351(k)(6)(c)(i)
[351] US Public Health Services Act at §351(k)(6)(c)(ii)

4.3.3. EU's Enhanced Data Exclusivity Regime

Adoption of a data exclusivity system in the EU was the result of intense lobbying by the pharmaceutical industry, citing the need to protect future investments leading to further innovation.[352] Enacted in 1965, the requirement for the provision of data in support of a new medicine application stems from Article 4.8 of the EU Directive 65/65/EEC.[353] The first iteration of EU's data exclusivity regime protecting the data mandated in 1965 was first implemented in 1987 in Directive 87/21/EEC; this Directive's main purpose was to establish bioequivalence as an evidentiary basis for the approval of generic pharmaceuticals.[354]

As patent law harmonization swept the globe through the adoption of GATT, WTO and TRIPs, as well as further European community expansion, patent regimes strengthen and pharmaceutical patent strategies rose in prominence. While it might be expected that with the rise of more powerful patent regimes, the need for increasingly broad data exclusivity would decrease; that was not the case.

The initial 1987 data exclusivity provisions provided for 6 years of data exclusivity for most medicines from the first marketing approval and 10 years for biotech products. If considered "in the interest of public health", member states were empowered to extend data exclusivity to 10 years; this crafted flexibility led to domestic variability across the EU. Importantly, EU states were also empowered to make the data exclusivity period and the date of expiry of a product patent (if allowed in the member state) coterminous.

[352] Medicines Law and Policy Guidance; Adamini, et al., JOURNAL OF HEALTH POLITICS, POLICY AND LAW, (2009).
[353] EU Directive 65/65/EEC
[354] EU Directive 87/21/EEC, revised in 2001 and 2004. Adamini, et al., JOURNAL OF HEALTH POLITICS, POLICY AND LAW, 980 (2009).

Broadened in 2004, the EU's data exclusivity regime is the most generous exclusivity regime globally,[355] embodied in two aspects: (1) the approval prohibition period in the EU is 10 years from the date of approval of the reference biologic, and (2) the filing prohibition period of 8 years during which time the EMA is precluded from accepting or reviewing any biosimilar applications for market authorization. Additionally, another 1-year period of protection is available where the reference biologic is approved for a new indication providing significant benefit during the filing prohibition period.[356]

4.4. Non-Patent Contentious Additional Protection Provisions Relevant to Biologics and Biosimilars

As discussed in the context of international treaty obligations in Chapter 3, the additional IP provisions are focused on compensation biologics manufactures for the loss of patent term due to the mandatory regulatory authorization assessment encroaching on their 20 year patent monopoly. Without yet having access to the market due to regulatory processes, the biologic applicant is precluded from commercially practicing its invention to the exclusion of others, thus precluded from leveraging its considerable innovation investment. As well, the compulsory data and evidence forming the basis of its obligation is generally conducted prior to the regulatory assessment process, also cutting into the patent term.

Two mechanisms have been crafted into the IP treaty obligations of Canada-US-Mexico FTA (2018) and Canada-EU FTA (2017) for Contracting Parties to alternatively adopt, namely provisions that either extend patent terms or *sui generis* rights that are analogous to, even depend upon, patent rights but do not directly affect the patents.

[355] Directive 2004/27/EC on the Community code relating to medicinal products for human use [2004] OJ L136/34. ("Data Exclusivity Directive"). The Data Exclusivity Directive required the adoption of domestic legislation.

[356] This additional year is also available where a drug is transferred from being prescribed to over-the-counter which is highly unlikely for a biologic.

Canada and the EU have implemented the latter – *sui generis* protection analogous to, depend upon, but not rights conferred by patents through Canadian Certificates of Supplementary Protection ("CSP") or EU's Supplementary Protection Certificates ("SPC"). The US, on the other hand, early on adopted the patent term extension ("PTE") approach initially with the enactment of the *Hatch-Waxman Act* applicable to pharmaceuticals. After some perceived ambiguity, the FDA has clarified that the US's Patent Term Restoration Program also applies to biologics.[357]

The purpose of PTE and CPS/SPC rights is to compensate biologic manufactures for the loss of patent term due to the mandatory regulatory approval process that demands the submission of expansive and expensive non-clinical and clinical trial evidence of the safety and efficacy of the biologic before it can be marketed.

The regulatory process in Canada, the US and EU takes years and often begins well after the filing date of relevant patents claiming the product, process or use related to the biologic under assessment. Thus, once granted, the 20-year patent term would be effectively curtailed because the compulsory regulatory process would be ongoing during the term of the patent; the biologic patent holder was precluded from commercially leveraging their patent (making, using, selling, offering to sell, or importing) until the biologic was approved for sale often years after the patent grant.

PTE and CSP/SPC regimes were a proposed solution to recoup some of the regulatory downtime by extending either the patent term (PTE) or providing protection analogous to patent rights beyond the expiry of the relevant patent (CSP/SPC) thereby compensating for the delay out of the control of the biologic applicant.

In addition to compensating biologics manufacturers for perceived current losses, PTE/CSP/SPC provisions would, in principle, further incentivize innovation and the development of new biologics.

[357] FDA FAQs

4.4.1. Canada's Certificates of Supplementary Protection System

Given a compensatory *sui generis* rights system was a treaty obligation arising from Canada-EU FTA (2017), it should come as no surprise that Canada's Certificate of Supplementary Protection ("CSP") is similar to the EU's SPC regime. Upon issuance, a CSP provides an additional period of protection of up to 2 years for new biologics protected by an eligible patent.[358]

The rights conferred by CSPs are codified in s. 115 of the *Canadian Patent Act* which provides that the scope of the CSP is the same as that of the patent, but only with respect to the making, constructing, using or selling of any drug [biosimilar] that contains the medicinal ingredient or combination of medicinal ingredients [biologic] set out in the CPS, by itself or in addition to any other medicinal ingredient.[359]

Like eligible patents listed in the context of Canada's PM(NOC) Linkage regime, CSPs are eligible to be listed in association with a biologic on the Patent Register pursuant to ss. 4(3.1) of the Canadian PM(NOC) Regulations which dictate two requirements. First, the patent noted in the CSP must be listed on the Patent Register in respect of the biologic. Second, the submission or supplement is in relation to a biologic with respect to which the CSP grants rights, privileges and liberties referred to in s. 115 of the Canadian *Patent Act*.

However, pursuant to s. 3(7) of the Canadian PM(NOC) Regs, no patent or CSP shall be added to the Patent Register until the drug (biologic) submission in respect of which the patent list was submitted receives an NOC. Once issued and listed on the Patent Register, the CPS protection lies dormant until the expiry of the patent set out in the CPS.

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[358] Canadian Patent Act 116(6). Government of Canada, Guidance Document Certificates of Supplementary Protection (Health Canada ed., 2 ed. May 2019). Pursuant to s. 166(3), the CSP term is calculated by subtracting five years from the period beginning on the filing date of the application for the patent and ending on the day on which the authorization for sale set out in the certificate is issued, but in any event is for a maximum of two years.

[359] Canadian Patent Act, s. 115

4.4.2. Patent Term Extension in the US

On the basis of statutory and jurisprudential interpretation, in addition to the position explicitly taken by the FDA, the patent term extension or restoration ("PTE") provisions enacted by §156 Title 35 of the *Hatch-Waxman Act* in 1984 apply to biologics. Specifically, under §156(f) of Title 35, PTE may be granted in respect of a human drug product defined as "…the active ingredient of a…human biologic product (as those terms are used in the…Public Health Services Act)…".[360]

A patent will only be eligible for PTE if it includes at least one claim encompassing the approved biologic (product claim), its process of manufacturing (process claim), or an approved use of the biologic (use claim). Further, the patent must satisfy the following criteria: (1) the cited patent has not expired; (2) the patent has not benefited from a previous PTE; (3) within 60 days of receiving the first marketing approval for the biologic from the FDA, the patent holder or its agent must submit a PTE application to the USTPO; (4) the biologic was subject to regulatory review period prior to its commercial marketing or use; and (5) the FDA's authorization is the first market approval of the biologic, or where the patented biologic manufacturing process primarily uses recombinant DNA technology, and the FDA's authorization is the first approval of a biologic that is manufactured under said patented process.[361]

In practice, both the USPTO and FDA participate in calculating and determining PTEs, but it is the PTO that makes the final determination on patent eligibility. For the purposes of this research, this process is non-contentious since the determination of PTE eligibility is based solely on the biologic manufacturer's representations set out in its PTE application; third-party communications will not be considered by the PTO outside an extraordinary situation.

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[360] Hatch-Waxman, Title 35 at §156(f). Biologics are approved under §351 of the Public Health Services Act, 42, USC, §262. The Bolar Exception in § 271(e)(1), adopted at the same time as §156(f), expressly applies to all biological human drugs.

[361] FDA FAQs, available at https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-patent-term-restoration-program

PTE have a maximum term of 5 years. The combination of eligible PTE term and the unexpired patent term cannot exceed more than 14 years or put another way, the biologic manufacturer cannot enjoy more than 14 years of market exclusivity.

The PTE term depends on the date of first marketing approval of the biologic. It is calculated by the difference between the first marketing approval date and the filing date of the patent in question, less 5 years. No PTE is available if less than 5 years have elapsed between patent filing and the first market authorization date.

The PTE term is less than 5 years if the difference between first approval date and the patent filing date is over 5 years but under 9 years, but beyond that difference, the PTE term is capped at 5 years. Accordingly, no patent term extension is available in respect of a biologic where there is 14 years or more left on the relevant patent term. Such a patent would be ineligible for PTE.

4.4.3. European Union's Supplementary Protection Certificates

In 1992, the EU introduced a *sui generis* right through the creation of Supplementary Protection Certificates ("SPC") providing up to 5-years of additional protection for pharmaceuticals protected by patent.[362] The purpose of this supplemental period of protection was to promote research and innovation leading to the development of new drugs, now including biologics, and to deter the migration of industry R&D efforts out of the EU to countries that might offer greater protection.[363]

[362] Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products OJ L 182, 2.7.1992, p. 1–5; SPC only had effect in countries that had product patents and not yet in countries where they were unavailable or had only recently introduced it. This regulation has been amended from time to time over the years effecting changes that are no pertinent to the current scope of research in this work.

[363] Regulation (EU) 2019/933 Of The European Parliament And Of The Council Of 20 May 2019 Amending Regulation (Ec) No 469/2009 Concerning The Supplementary Protection Certificate For Medicinal Products At Preamble Para. 2

Under this regime, SPCs extends protection over eligible biologics required to go through the EU's regulatory authorization process[364] that are protected by product, process and/or use patents, but are not themselves patent rights. SPCs seek to mitigate the potential harm arising from the effective reduction of patent protection terms due to the long and mandatory regulatory process. This justification for EU's SPC system remains consistent with the Canadian justification for its relative new Certificate of Supplementary Protection regime, as well as US' patent term restoration provision now just over three decades old.

Interestingly, an amendment specifically targeting biosimilars was adopted recently which created two manufacturing-based exceptions to SPC protection in the 6 months prior to its expiry.[365] The exception of particular pertinence allows a biosimilar manufacturer the ability to manufacture biosimilar, otherwise precluded by the SPC, for the purpose of storage so that the biosimilar will be ready for market launch immediately after the expiry of the SPC.

This exception was to even the playing field between EU-based manufacturers vs. foreign manufactures who would be ready to launch immediately upon the SPC expiry having had the ability to develop manufacturing capacity by being unburden by the SPC.[366]

A biosimilar applicant must meet certain criteria to rely on the storage use exception: (1) at least three months prior to commencing the otherwise offending acts, the biosimilar applicant must notify the SPC holder of prescribed information related to the

[364] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).
[365] Regulation (EU) 2019/933 Of The European Parliament And Of The Council Of 20 May 2019 Amending Regulation (EC) No 469/2009 Concerning The Supplementary Protection Certificate For Medicinal Products. This legislation came into force on July 1, 2019. Initially, the exception will apply to SPCs that are applied for on or after July 1, 2019. From 2 July 2022, it will also apply to SPCs that were applied for before 1 July 2019, but only if they had not taken effect before 1 July 2019.
[366] Regulation (EU) 2019/933 Of The European Parliament And Of The Council Of 20 May 2019 Amending Regulation (EC) No 469/2009 Concerning The Supplementary Protection Certificate For Medicinal Products at preamble para. 4, 5, 6, 7, and 8

biosimilar to be manufactured under this exception as well as provide the same information to the Member State's intellectual property office; (2) the patent cited on the SPC application has not yet expired as of the date of the SPC application; (3) the SPC is filed in respect of the first market authorization grant for the relevant biologic in the Member State; (4) the patent cited in the SPC application is not subject to a previously granted SPC in the Member State.

The protection conferred by the SPC is not an extension of the patent term or any other patent rights; SPCs extend the effect of the right namely, the right to exclude others from practicing the invention. Thus, an SPC extends the market exclusivity of a biologic, preluding a biosimilar being granted market authorization until the expiry of the SPC.

Importantly, the SPC only comes into force upon the expiry of the cited patent for, in the normal course, a period of 5 years. Given the formula for calculating the SPC term, the total combined term of market exclusivity granted by virtue of both patent and SPC protection cannot normally exceed 15 years. [367]

The SPC term depends on the date of first marketing authorization and is calculated as the difference between that date and the filing date of the relevant patent less 5 years. Normally, this means that no SPC term is available if less than 5 years have elapsed between the patent filing date and the first market authorization date. Presumably, the biologic manufacturer has not suffered undue delay in the marketing authorization process that the SPC was created to protect against in this scenario.

Undue delay apparently kicks in if the first marketing authorization date is over 5 years but under 10 years after the patent filing date; the SPC term then corresponds to the period elapsed between the five-year point and the first marketing authorization date representing the undue delay the SPC seeks to address. Ultimately, the SPC term is

[367] SPC protection term may be extended for an additional 6 months where the SPC relates to a biologic for which data from clinical trials conducted in accordance with an approved Pediatric Investigation Plan (PIP) have been submitted, as set forth in Article 36 of Regulation (EEC) No 1901/2006. This leads to a 5.5 year SPC term and 15.5 year combined patent and SPC term, respectively, in the normal course.

capped; SPC protection for biologics where the first marketing authorizations are granted more than 10 years after the patent filing date is 5 years.

SPC protection is mandated in all EU and EEC Member States, but these regimes are not unified or even mutually recognized; SPC applications must be filed and approved on a state by state basis tracking to the different dates of first market authorizations, even if based on the same underlying patent.

4.5. Summary of Chapter 4

Chapter 4's examination of the ways in which each of Canada, the US and EU have implemented their respective treaty obligations. Canada's implementation of its treaty obligations, in particular its patent linkage regulations, is an exercise of discretion that has led to a different approach in Canada that, as will be explored in Chapter 5, serves to impede the number and timely entry of biosimilars on to the Canadian market.

On the face of the quantitative analysis, a marked difference in the number of biosimilars approved and marketed in Canada (and the US) in comparison to the EU is observed. While Canada adopted an assessment framework prior to the US, it has slightly lagged in its approval numbers, but interestingly its market launches are faring better than their American counterparts. Consideration of the reasons for these quantitative results will be of particular interest in Chapter 5's analysis and discussion.

CHAPTER 5. Analysis and Discussion

5.1. Introduction

The central question explored in this work centers on the impact of how Canada has chosen to craft its legislation and regulations domestically in furtherance of its international treaty obligations on the regulation of biosimilars, linked to patent/IP considerations, in comparison to the US and the EU.

Without question, the EU has enjoyed significant success in the implementation and execution of its biosimilars strategy which may be in part because of the head-start that it has had in the regulation of biosimilars in comparison to the US and Canada, but as will be explored in this Chapter, that is far from the entire picture.

There are some very interesting comparisons to be drawn upon reflection of the number of approved biosimilars in relation to (1) the coverage of reference biologics, namely how many "follow-on" biosimilars per reference biologic and (2) how many have been launched on the market. The target reference biologics seem to be based on patent expiry dates and the size of the market, which, I surmise, address two important factors: risk and reward.

As explored herein, it is the second factor, namely the prominence of patent considerations, that form the main basis for the discrepancies between the EU versus the US and Canada. In essence, the way that Canada (and the US) implemented its international obligations, in particular patent linkages, has contributed to the delayed adoption of biosimilars and their launch on the Canadian market.

The interplay of patent litigation in the US and Canada through their respective patent linkage regimes is complicated by biologic patent strategies that create clusters of patents or "thickets" that provide intertwining coverage creating overlapping and potentially overreaching entitlements that may eventually prove to also be overbroad.

These patent thickets provide dense coverage of the "core" claims attracting patent linkage protection, as well as peripheral patents focused on non-eligible claims.

US litigation is further hampered by (1) a lack of patents listed in the Purple Book and (2) the inherent uncertainty of the patent dance, both of which may be factors in the increasing incidence in settlements delaying the launch of the biosimilar years after the grant of approval.[368]

In Canada, the recently overhauled Canadian patent litigation framework shifting from *in personam* applications to *in rem* actions has had the likely unintended consequence of further integrating the Canadian biosimilar outcomes with US outcomes in terms of settlement agreements that are not yet subject to additional governmental scrutiny. Further, Certificates of Supplementary Protection are in effect proxies or carry on rights that are challenged in the same way patents are challenged in Canada. In particular, CSPs are integrated into the Canadian patent linkage Regime in a way that has not happened in the EU.

In terms of data exclusivity, the provisions that created a tight assessment window for biosimilar applications may serve to unjustifiably delay the approval of biosimilars beyond the expiry of the data exclusivity period in the future. However, as concluded from an examination of the relevant reference biologics, data exclusivity has yet to be triggered in the assessment of a biosimilar in any of the US, EU, and Canada to date.

As will be established in this Chapter, the factors noted above and addressed in more detail below are not mutually exclusive; they are intertwined and dynamic systems layering obstructions with the cumulative effect of precluding the entry of biosimilars into the Canadian market to the detriment of Canadian patients and the public and private payers' bottom line.

[368] Daniel Gervais, *The Patent Option*, 20 NORTH CAROLINA JOURNAL OF LAW & TECHNOLOGY (2018).

Undoubtedly, it is in the best interest of the Canadian public, and humanity writ large, to promote the creation of innovative biologics, an enormously resource heavy and expensive endeavour primarily funded by private industry players. Similarly, it is equally important to incentivize further innovation as well as encouraging healthy competition by promoting the development and adoption of biosimilars. A better balance can and needs to be struck.

5.2. The Numbers – Quantitative Analysis and Assessment of Market Authorized Biologics and Biosimilars

To gain insight into the effect that Canada's national implementation of its international obligations has had on biosimilars, a quantitative analysis of the biosimilars approved and launched to date is undertaken. We look at the success of biosimilar approvals and their availability on the Canadian market as a measure of how Canada is faring in this important step to bring biosimilars to Canadians and what aspects of its national implementation arising from progressive patent and regulatory obligations may be hindering biosimilar approval and launch.

Data in respect of the biosimilar approvals and launches in Canada, the US and EU are presented in Appendices 1-3 which form the basis for the following findings. Data reported in Appendix 4 represents an amalgamation of some of the data reported in Appendices 1-3 that contextualizes this information to gain further insight into the effects that Canada's implementation of its international treaty obligations has had on biosimilar approval and marketing. All data was obtained from searches of either the national databases maintained by each jurisdictions' respective agencies or public sources such as press releases and news reports.

Turning first to the Canadian numbers: the Canadian Drug Product Database provides comprehensive information about biologics and biosimilars that have been granted market authorization. Broken down by status, the Drug Product Database lists biologics

and biosimilars that are marketed,[369] approved,[370] cancelled post-market,[371] cancelled pre-market,[372] cancelled pre-market for a variety of safety issues,[373] or cancelled for administrative reasons[374] or dormant.[375]

The details of the Canadian experience is set out in Appendix 3. To date, there are 24 approved biosimilars making reference to 11 reference biologics,[376] two of which have yet to launch, in Canada. As it now stands, there are no IP holds or stays pending litigation that is impeding the market launch of the following biologics. Currently, there are no biologics or biosimilars that have been cancelled pre-market on the basis of a safety issue, nor have there been any cancellations on the basis of an unfiled Annual Notification. On the face of these numbers, biosimilars approvals are overall faring better that those in the US, but not as well as the in the European regime.

Like the comprehensive information made publicly available by Health Canada, the US Food and Drug Administration's Purple Book lists all of the biosimilars that have been approved by way of the abbreviated pathway for biosimilars pursuant to §351(k) of the

[369] Marketed refers to an active DIN that is currently being sold in Canada.
[370] Approved refers to an active DIN that has been reviewed and authorized for sale in Canada but has not yet been marketed in Canada.
[371] Cancelled Post-Market refers to a DIN that is cancelled further to the discontinuation of the sale by the manufacturer pursuant to Section C.01.014.6 (1)(a) of the Canadian FDA Regs.
[372] A distinction is made between DINs that are cancelled before it was ever marketed in Canada, namely cancelled pre-market, rather than those that were cancelled pre-market due to safety issues.
[373] Such as failure to provide evidence regarding the safety and effectiveness of a drug, under Section C.01.013 of the Regulations pursuant to Section C.01.014.6 (2)(b) of the Canadian FDA Regs, the suspension of and Notice of Compliance under section C.08.006 pursuant to Section C.01.014.6 (2)(b) of the Regulations, failure to comply with the order issued under section 21.31 of the Act to conduct an assessment and provide the results pursuant to Section C.01.014. 6 (3)(a) of the Regulations, and following the examination of the results of an assessment provided in response to an order issued under section 21.31 of the Act pursuant to Section C.01.014.6 (1)(a) of the FDARegs.
[374] Canadian Food and Drugs Act s. C.01.014.6(2)(a). for failure to file an Annual Notification pursuant to C.01.014.5.
[375] Dormant refers to an active DIN that was previously marketed in Canada but for which there have been no sales for period of at least 12 months. See DPD Database reference terms.
[376] AVASTIN (bevacizumab), ENBREL (etanercept), GENOTROPIN (somatropin), HERCEPTIN (trastuzumab), HUMALOG (insulin lispro), HUMIRA (adalimumab), LANTUS (insulin glargine), NEOPOGEN (filgrastim), NEULASTA (pegfilgrastim), REMICADE (infliximab), RITUXAN (rituximab). Each of these reference biologics have been granted market authorization in Canada. While Canadian biosimilar applicants are statutorily permitted to rely on data and information submitted before aanother non-Canadian regulatory agency, no biosimilar applicant has yet availed themselves of this option to date. We are still in early days and that day might yet still come to pass.

US Public Health Services Act. As set out in Appendix 1,[377] 28 biosimilars have been approved making reference to 9 reference biologics.[378] However, 10 of these biosimilars have not launched. Eight biosimilars (6 biosimilars of HUMIRA (adalimumab) and 2 biosimilars of ENBREL (etanercept)) were first delayed by litigation and now presumably as a result of settlement agreements reached between AbbVie and all of the biosimilar applicants seeking market authorization. These private arrangement have concerning implications as discussed below.

Similar to its place as the pioneering jurisdiction in the regulation of biosimilars, the European biosimilar approval and marketing numbers surpass Canada and the US. Sourced from the European Medicines Agency's medicines database,[379] the assessment detailed in Appendix 2 shows that 65 biosimilars have been approved making reference to 15 reference biologics.[380] A number of these biosimilars have been withdrawn for a variety of reasons. However, none of the reasons are attributable to litigation delays or even delays due to data exclusivity periods of supplementary protection certificates. Further, there are currently a total of 16 biosimilars under review in the EU, two of which are the first biosimilar in relation to new reference biologics that previously had no biosimilar.

This analysis of biosimilars approved and launched provides a measure of the impact of Canada's implementation of international obligations to determine whether and how the differences in the way Canada has implemented patent linkages, data exclusivity and additional IP provisions have impacted the market entry, or lack thereof, of biosimilars in comparison to the US and EU. But what do these numbers actually mean?

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[377] Current to July 31, 2020

[378] AVASTIN (bevacizumab), ENBREL (etanercept), HERCEPTIN (trastuzumab), HUMIRA (adalimumab), NEUPOGEN (filgrastim), NEULASTA (pegfilgrastim), PROCRIT (epoetin alfa), REMICADE (infliximab), RITUXAN (rituximab)

[379] Current to July 31, 2020

[380] AVASTIN (bevacizumab), ENBREL (etanercept), EPREX/ERYPO (epoetin alfa), FORSTEO (teriparatide), GENOTROPIN (somatropin), GONAL-F (follitropin alfa), HERCEPTIN (trastuzumab), HUMALOG (insulin lispro), HUMIRA (adalimumab), LANTUS (insulin glargine), LOVENOX (enoxaparin sodium), MABTHERA (rituximab), NEOPOGEN (filgrastim), NEULASTA (pegfilgrastim), REMICADE (infliximab)

What bearing do they have on the questions of progressive international treaty obligations and the variability of their national implementation?

There are some very interesting comparisons to be drawn upon reflection of the number of approved and launched biosimilars in relation to (1) the clustering of reference biologics, namely how many "follow-on" biosimilars per reference biologic, (2) the number those biosimilars that have been launched and not launched on the market, and (3) the reason, actual or speculative, that the unlaunched biosimilars have been precluded from market launch. This analysis will assist in understanding the consequences of Canada's choices in its implementation of treaty obligations in light of the goals of promoting access to cost-effective cutting-edge therapeutics for the good of Canadians while at the same time promoting the innovation of new biologics.

In the context of this work, biosimilar "clustering" refers to the number of biosimilars that make reference to the same biologic. The EU as the outlier reports the approval of 65 biosimilars, of which the vast majority have been or are currently available on the market. Very interestingly, the cluster of biologics has been relatively broader for a longer period of time, coming in at a total of 15 reference biologics.

In contrast, the Canadian ratio of biosimilars that are approved, marketed and clustered to reference biologics is 24:22:11. The picture in the US looks quite similar: 28 approved biosimilars making reference to 9 biologics, but the biggest difference is in the launch numbers. Thus, the comparable ratio yields 28:18:9. In both Canada and the US, there is significant overlap or clustering of reference biologics; the biosimilars make reference to 9 and 11 reference biologics are almost identical, but for 2 that are available in Canada. However, the distinction evident in the American context is the number of biosimilars that, while approved, have yet to launch. The majority of these biosimilars were first delayed due to patent litigation, but are now presumably precluded from the market – *both Canadian and US markets* – by private settlement agreements. Of the 10 biosimilars that have yet to launch in the US, 8 are delayed for years due to patent

litigation settlements and licensing agreements reached between the biologic and biosimilar manufacturers in respect of HUMIRA (adalimumab) and ENBREL (etanercept).

Turning to Appendix 4, further insight can be gained when comparing the success of the approval and launch in the EU to the deficiencies in the US and Canada. First, Canada (as well as the US) lags behind the EU in the number of biosimilars approved which cannot be solely attributable to the length of time that the EU has been approving biosimilars (since early 2000s) versus the evolution of Canada's regulatory scheme creating an abbreviated pathway for biosimilars a decade later.

Second, not only are more biosimilars approved and launched in the EU, but both approvals and launches tend to happen sooner in the EU rather than both Canada and the US.

Third, there is a clustering of target reference biologics – i.e., the propensity for multiple biosimilar applicants to target the same reference biologic – in Canada and the US, but there appears to be a longer standing trend in differentiation in the EU.

Finally, in the EU there tends to have more biosimilars approved and launched per reference biologic. This further competitive pressure on the biologic, as well as the other competing biosimilars will ultimately result in decreased prices to the benefit of patients and payers alike.[381]

With these conclusions regarding the numbers of biosimilars approved and launched in Canada, as compared to the US and EU, the remaining discussion will turn to the reasons underpinning these moderately concerning trends in Canada and recommendations to mitigate the harm inherent in the current and interrelated patent linkage, data exclusivity and additional IP regimes.

[381] Daniel Acquah, *Extending the Limits of Protection of Pharmaceutical Patents and Data Outside the EU – Is There a Need to Rebalance?*, 45 IIC - INTERNATIONAL REVIEW OF INTELLECTUAL PROPERTY AND COMPETITION LAW 256(2014).

5.3. The "Ratchet" Effect – Canada's Detrimental Implementation of its International Treaty Obligations Regarding Biosimilars

Adoption of the early working/Bolar exceptions in the US and EU, set the stage to normalize the exceptional status of pharmaceutical inventions providing justification for governments to treat them differently than every other technology. The early working exception was the first step in the successive escalation of and deviation from traditional patent and other IP laws and policies in relation to pharmaceuticals, then biologics.

Canada's implementation of its treaty obligations have consistently lead to the increase in complexity and stringency of its national standards rather than being primarily dictated by the national considerations of patient care, best treatment practices, and cost efficiencies. This is especially telling given Canada's history with the compulsory licensing regime giving rise to a strong generic industry. The pendulum swung, but did Canada swing it too far? Maybe, given that many of the changes dictated by the international trade agenda, echoed by Canadian industry brand stakeholders owing allegiance to their US or European parent companies, have resulted in the implementation of increasingly strict national constructs than was necessarily required by its international obligations as examined in this work and further in this section.

In an effort to promote generic pharmaceuticals,[382] bringing with it the promise of more affordable drugs, Canada, the US and EU implemented early working/Bolar exceptions thereby allowing generics authorization to do that which would otherwise be prohibited.[383] So during the term of the brand's patent, a generic was able to practice the invention and develop a generic version of a patented brand drug that was also subject to data exclusivity protections.

[382] Promote, but not *enable* generic manufactures as much as Canada's abolished compulsory licensing regime had done in the preceding decades.
[383] Claims to pharmaceutical products or processes were not prohibited from protection in these jurisdictions in Canada, the US and EU at least as late as post-1993.

In an effort to strike a balance for giving generics this "head start", protections arising from patent linkages and data exclusivity were extended to brands. But it did not stop there. Over time, in the name of striking the appropriate balance, Canada has experienced a "ratcheting" up phenomenon as tweaks were made to Canadian patent laws and regulations at the behest of international trade agendas.

In Canada, the attempts to strike a balance between the brand and generic pharmaceutical companies, now in respect of biologics and biosimilars, have simply served to increase the competing protections such as patent eligibility which has experience a tightening of the types of eligible patents, increased data exclusivity stringency and created a whole new set of rights analogous to patent rights again in the name of balance. Specifically, this progression is demonstrated in the evolution of data exclusivity, as well as the significant changes that the Canadian PM(NOC) Regulations has undergone since their inception and integration with the early working exception through s. 55.2 of the Canadian Patent Act.

A similar situation has also played out in the US in terms of its patent linkages as well as an incrementally increased scope of data exclusivity to 12 years for biologics well beyond the protection given to pharmaceuticals. However, it should be noted that efforts are afoot in the US to push back against the "ratcheting" incremental increase of US data exclusivity. Calls to include a 10 year data exclusivity minimum in Canada-US-Mexico FTA (2020) led to the unilateral withdrawal of this provision by the US prior to ratification.[384]

Canada, however, accepted the increase to the data exclusivity period to 10 years dictated by the Canada-US-Mexico FTA seemingly without objection before it was unilaterally removed by the US. Canada regularly follows the steadily increasing international obligations which are then matched by national legislation that often goes beyond what is stipulated in international agreements. There does not seems to be a

[384] Admittedly, this is different from the current 12 year approval prohibition period in the US, but dialing back an international obligation is not the same as amending domestic legislation.

specific reason why Canada regularly goes beyond its obligations, but one possibility is Canada's propensity to want to please its trading partners as a result of the differential power imbalance, as well as being susceptible political and industry pressures.

As addressed more fully in the section below, however, the most notable detrimental aspect of American biologics patent litigation is the lack of patents listed the Purple Book.

5.4. Patent Thickets and Linkages – Death by a Thousand (Patent) Cuts

The existence of patent linkage regimes is a strong indicator of delayed biosimilar approvals and, going a step further, acts as a deterrent on biosimilars development; a deterrent that is compounded with the uncertainty in the number and scope of patents that may be at issue. In the EU, there is no direct link between the regulatory approval of biosimilars and reference biologic patent clearance; however, an indirect connection through Supplemental Protection Certificates tied to patent rights exist, but are addressed at the agency level, not through litigation.

The situation in the US and Canada is similar; there is a comparably lower number of biosimilars approved for a similar reference biologic cluster in comparison to the EU. However, these lower numbers may not be attributable solely to the EU's decade or so head-start given that the relevant patents related to the approved biosimilars had comparable patent expiry dates which, even absent a patent linkage regime, would have served to curtail commercially risky behaviour.

Recall, in both Canada and the US (where patent linkages are material considerations) there are mechanisms for the identification of patents that are potentially asserted against a biosimilar which must be addressed prior to market approval of the biosimilar.

In order to be eligible for listing on the Canadian Patent Register, a patent must contain a claim to the medicinal ingredient, a claim for the formulation containing the medicinal ingredient, a claim for the dosage form or a claim for the use of the ingredient.[385]

Similarly in the US, but only in the pharmaceutical context, patents are listed in the Orange Book that relate to (1) the compound patent (covering the pharmaceutical active ingredient), (2) product patents (formulation and composition) and (3) method-of-use patents (indications).[386] However, the most notable deviation from the pharmaceutical patent linkage regime is the differences in the Purple Book, the analogous but certainly not identical register of biologics and biosimilars.

The Purple Book is silent as to the patents applicable to a given biologic. Why were patents overlooked when the Purple Book was created? Well, they were not overlooked at all; their inclusion was specifically rejected. The bargaining position of stakeholders, namely the brand pharmaceutical industry, at the time the Orange Book was crafted in the early-80s was far different than in 2010. It is likely that attempts to make changes to this state of affairs will ultimately prove successful, but every day of exclusivity on the market for a multi-billion dollar drug is a good day for its manufacturer until that time comes.

The Purple Book's deficiencies are coupled with the ineffectual patent dance during which time the parties are to come to some accommodation in respect of the patents at issue between the parties. The most recent judicial statement from the US Supreme Court is that parties cannot be sanctioned outside of the measures already statutorily provided so the recourse is the patent litigation that the parties were heading towards in any event.

The lack of clarity on the identity of the patents that may ultimately be asserted by the reference biologic holder against the biosimilar applicant is compounded by the

[385] PM(NOC) Regulations at s. 4. Section 4.5.1 of Canada, Guidance Document Patented Medicines (Notice of Compliance) Regulations. May 11, 2018.
[386] FDA Regulations at 21 C.F.R. § 314.53(b)(1)

deliberate cultivation of patent thickets creating another layer of exclusion. Biologics are designed to be highly targeted, efficacious against diseases historically difficult and expensive to treat like cancer, diabetes, rheumatoid arthritis, and other inflammatory conditions.[387] Given that the technology to develop these treatments are themselves fairly recent developments, they themselves give rise to patentable technology.

Pharmaceutical patents are not properly characterized as "thickets" since the patent mass is much smaller by comparison owing to the less complex nature of these agents, and developers have been aided by the FDA's Orange Book, which includes exclusivity information along with product formulation data. Patents covering biologics, however, are statistically higher in number than comparable in the pharmaceutical context.[388] Couple this trend with the increased number of patents that are related to other innovative aspects of the biologic, such as new cell lines, innovation in cultivation or purification, and the terms "patent thicket" or "patent maze" become more apt.

Patent Thickets refer to a mass of patents where the inventions are likely overlapping, have readily apparent validity challenges based on lack of novelty or overbreadth, and contribute to an uncertain patent landscape where boundaries are difficult to ascertain – a thicket which is difficult to assess and navigate a path through.[389] For instance, patents related to the core inventions in respect of two top biologic products in the top 10 list of highest revenue products, are each covered by 93 (HUMIRA) and 43 (RITUXAN) core patents respectively.[390] The core patents covering similarly situated pharmaceuticals are 7 and 3.[391] Thus, there is a vast amount of uncertainty in ascertaining the patent and regulatory landscape of a reference biologic that is itself a bar to the identification and development of biosimilars.

[387] Chen, et al., DRUGS, (2018).
[388] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019).
[389] Id. at.
[390] Id. at.
[391] Lyrica and Eliquis; id. at.

The implications of this shift from PM(NOC) Application to PM(NOC) Action has not yet been made clear. The first judgement of the Federal Court of Canada arising from a PM(NOC) Action was rendered only on April 16, 2020 in Amgen Inc. v. Pfizer Canada ULC in respect of Pfizer's biosimilar NIVESTYM (filgrastim) making reference to Amgen's NEUPOGEN (filgrastim). [392] Further, the academic literature is sparse. The legal commentary from the private practice community reiterates the Canadian government's rationale to strike a balance by mirroring traditional patent litigation to achieve the objectives of providing a route of appeal, eliminating dual litigation, enabling parties to advance a full record based on discovery and viva voce evidence. In relying on experience, the advantages of the shift from an application regime to an action regime is significant, but not for reasons related to the stated objectives. Framing Canada's patent linkage regime as *in rem* actions allows for and makes more attractive private settlement agreements between parties that can serve to delay the market launch of biosimilars. In the PM(NOC) Application regime, the *in personam* and dual nature (i.e., application, then potential subsequent action) of these proceedings did not lend well to making multiple deals with competing biosimilar applicants. As well, the reference biologic applicant could assert the validity of patents in multiple proceedings given that any findings were non-binding as between applications. However, with the potential of a finding of invalidity looming, it would stand to reason that a reference biologic holder would seek to protect its patent in Canada, as well as in other jurisdictions, and be inclined to settle proceedings against competing biosimilars in order to preserve its market share for as long as possible. Biosimilar applicants would also view this approach favourably by avoiding costly litigating and potentially securing market entry to the advantage of other biosimilar applicants.

By way of illustration, litigation involving oncology targeted HERCEPTIN (trastuzumab) and RITUXAN (rituximab) deals with 52 Genentech patents, most of which are not core

[392] 2020 FC 522.

patents, but are peripheral that relate to manufacturing, such as making cells, cell culture media, and protein purification.[393]

As previously noted, there are over a hundred patents covering HUMIRA (adalimumab), many of which were granted well after the biologic's launch, but many of these peripheral patents are for methods of manufacture or use, as well as additional unauthorized indications that should not pose a bar to market authorization.[394]

A number of biosimilars have targeted seeking even just a piece of the almost $20B market. The product patents on adalimumab expired in the US in December 2016 and in Europe in June 2017.[395] However, in the US AbbVie has taken the staunch position that while their product patent has expired, other patents covering inventions related to HUMIRA (adalimumab) do not expire until no earlier than 2022. Instead of protracted litigation on multiple fronts, AbbVie executed a successful licensing and settlement strategy that preserves it exclusivity and likely provides a licensing revenue stream without risk to having its patents' validity challenged. Accordingly, of 10 biosimilars that have been approved but not launched in the US, 6 are biosimilars of HUMIRA (adalimumab)[396] where all of the biosimilar applicants have negotiated private settlement agreements,[397] likely including license payments, to enter the market sequentially beginning in 2023.[398]

Two ENBREL (entanercept) biosimilars[399] remain subject to litigation which apparently involve 5 or fewer patents, "depending on whom you ask…".[400] This litigation will likely

[393] Hagen. March 14, 2020.
[394] Wu & Cheng, CHI.-KENT J. INTELL. PROP., (2019).
[395] Derbyshire M. Patent expiry dates for biologicals: 2018 update. Generics and Biosimilars Initiative Journal (GaBI Journal). 2019;8(1):24-31. doi:10.5639/gabij.2019.0801.003
[396] AJEVITA (adalimumab-atto); CYLTEZO (adalimumab-adbm); HYRIMOZ (adalimumab-adaz); HADLIMA (adalimumab-bwwd); ABRILADA (adalimumab-afzb); HULIO (adalimumab-fkjp).
[397] European Pharmaceutical Review, *Patent litigation for adalimumab resolved in the US*, European Pharmaceutical Patent Review(May 24 2019), *available at* https://www.europeanpharmaceuticalreview.com/news/88877/abbvie-patent-boehringer-ingelheim/.
[398] Mehr, (2020).
[399] ERELZI (etanercept-szzs); ETICOVO (etanercept-ykro)
[400] Hagen. March 14, 2020.

keep entanercept biosimilars off the market until 2029 in light of the recent US Disctrict Court of New Jersey's ruling in favour of Amgen's ENBREL (etenercept-szzs) against Sandoz' biosimilar ERELZI (entanercept).[401] Sandoz acknowledged that "[valid] intellectual property should be respected, however, we continue to consider the patents, in this case, to be invalid…"[402] The two patents that were upheld were exclusively licenced to Amgen by Roche, however the original product patent expired as long ago as 2012. Roche's patents are a good example of the effect of the patent thicket effect extending Amgen's market exclusivity until 2029.[403] Amgen is similarly excluding Samsung Bioepis' previously approved ETICOVO (entancercept-ykro) from the market through patent litigation.[404]

Of the remaining 2 approved but unlaunched biosimilars: 1 is not coming to market because of business reasons,[405] and the last was approved only in June 2020.[406]

From the Canadian perspective, the American patent linkages and patent thickets undoubtedly affects the Canadian litigation experience since pharmaceutical and biologic patent litigation is highly coordinated and invariably dictated from the US. Further, there is a propensity to cede less valuable jurisdictions in an effort to protect more valuable markets. The circumstances leading to the discontinuance of PM(NOC) Actions may not be disclosed unless done so by the parties, the same is true for any terms such as settlement agreements or licensing agreements. Thus, it is possible for

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[401] Victoria Rees, *Amgen wins court patent ruling over Sandoz biosimilar*, EUROPEAN PHARMACEUTICAL REVIEW August 13, 2019. 2019.

[402] Kelly Davio, *In Long-Awaited Decision in Etanercept Litigation, Court Sides With Amgen Over Sandoz*, *available at* https://www.centerforbiosimilars.com/news/in-longawaited-decision-in-etanercept-litigation-court-sides-with-amgen-over-sandoz.

[403] Richard Staines, *Three years after approval, court blocks US launch of Enbrel biosimilar* (August 12, 2019), *available at* https://pharmaphorum.com/news/three-years-after-approval-court-blocks-us-launch-of-enbrel-biosimilar/.

[404] Immunex Corp. v. Samsung Bioepis Co., Ltd. , 2:19-cv-11755 (D.N.J.); Benjamin R. Holt, *Another Biosimilar Receives FDA Approval and Is Confronted with Litigation* (April 25, 2019), *available at* https://www.biosimilarsip.com/2019/05/28/another-biosimilar-receives-fda-approval-and-is-confronted-with-litigation/.

[405] IXIFI (infliximab-qbtx). Pfizer is committed to another of its infliximab biosimilars, INFLECTRA (infliximab-dyyb) developed and manufactured with Celltrion, Inc.

[406] NYVEPRIA (pegfilgrastim-apgf) Sauer comments

litigation to proceed in the US while terms are reached in Canada allowing the biosimilar to proceed to market, likely under some kind of royalty arrangement, or simply have the Canadian litigation bundled up with the US settlement. For instance, the biosimilar HADLIMA (adalimumab)'s launch is delayed by agreement in the US which is likely to also cover the Canadian litigation discontinued on April 10, 2018, but not made public. Similarly, for the unlaunched RIXIMYO (rituximab), a discontinuance was filed on November 21, 2018 and the biosimilar remains unlaunched, for how long is only known to the parties to the settlement agreement.

Finally, the faster approval and market launch in the EU bears some consideration. In the EU, it is quite common for products to be launch fairly quickly after approval has been granted, likely due to the fact that IP clearance occurs at the regulatory level and is primarily a result of an assessment of data exclusivity and Supplementary Protection Certificates. data exclusivity regimes are not normally subject to litigation, but may be subject to challenge at the regulatory level. Supplementary Protection Certificates are tied to underlying patents and may be revoked where a patent has been found to be invalid, but again, there is no direct linkage to the EMA's regulatory assessment with the clearance of patent rights through a patent linkage regime.

There are multiple calls to reform the Purple Book to address the information disclosure imbalance between the biologics and biosimilar companies. Indeed, there are more formal actions at play seeking to statutorily compel the disclosure of patent and exclusivity information, namely the *Purple Book Continuity Act of 2019*.[407] Similarly, the draft *Biologic Patent Transparency Act* tabled by senators US Susan Collins and Tim Kaine, represents a strong statement about seeking to "put an end to the harmful

[407] Davio, Congress Votes on Amending Orange and Purple Books in Effort to Encourage Generics and Biosimilars May 8, 2019;Generics and Biosimilars Initiative, *FDA's Orange and Purple Books to be improved and updated Posted 31/05/2019*, Generics and Biosimilars Initiative(May 31, 2019), *available at* http://www.gabionline.net/layout/set/print/content/view/full/9707;Cook. May 7, 2019.

patent strategies that block new drugs from coming to market".[408] The rhetoric is strong on both sides. While it is not likely that either of these bills will pass in their current form, the undercurrent speaks to a need for change.

Prioritizing assessments based on markets where you can get authorized quickly with minimal litigation exposure are business strategies for private sector players; for those entities beholden to shareholders, it is not a question of where the biologic can most impact patients' outcomes and public and private healthcare costs. And that's understandable. What is not understandable is for governments to be complicit in the continued obfuscation of the patent landscape precluding biosimilars from the same transparency afforded to the brand/generic pharmaceuticals players versus the same players in the biologic/biosimilars context. While one might argue that this unfairness falls solely within American borders – Canada has a functioning patent list after all – this would represent a severe misunderstanding of the level of interconnectedness of patent litigation, or rather US "directedness".

At a high-level, there are good reasons to promote settlement between litigants. Uncertainty in the patent landscape falls away, significant resources and money can be better employed elsewhere, and a way forward for all parties becomes known. However, where the terms of settlement between private companies have such significant impacts on the public health and public money, perhaps some additional scrutiny of these agreements that negotiates prolonged market exclusivity arrangements is warranted.

What does all of this mean? It means that Canada has implemented its international obligations through the adoption of a patent linkage regime that allows for confidential settlements delaying market entry of biosimilars on conditions that have nothing to do with their regulation. It means that private enterprise, not necessarily even Canadian, is

[408] David Wallace, *US Bill Aims To Increase Transparency On Biologics available at* https://generics.pharmaintelligence.informa.com/GB140140/US-Bill-Aims-To-Increase-Transparency-On-Biologics.

dictating by secret agreements the public's access of biosimilars, the launch of which will have a profound impact on the price and patient access of critically important and wildly expensive drugs. And, from a Canadian perspective, many of these considerations apply to Canada as an afterthought given that many strategic decisions are with the US market in mind and settlements delaying market entry of a biosimilar generally apply to multiple jurisdictions, if not worldwide.

5.5. Canada's Data Exclusivity Regime – Its Current Irrelevance and Potential Imbalance

Canada has had to implement changes to its data exclusivity regime in response to its international obligations which have progressively increased in complexity and stringency, both of which have not been balanced against increased efficiency in the regulatory approval process.

However, the practical operation of these provisions have yet to be tested because to date, Canada's data exclusivity regime has yet to be engaged in the course of the regulation of any of the 24 approved biosimilars. Indeed, the situation is identical for the US and the EU. Recall, the data exclusivity periods canvassed in Chapter 4 stipulate the ultimate expiry of the data exclusivity periods 12, 10 and 8 years after the date of first authorization in Canada, the US and EU, respectively.

The national effect on biosimilar applications was ascertained by determining first if the date of any of the biosimilar approvals making reference to the noted reference biologic was within 5 years[409] of the expiry of the each respective Market Prohibition Period. If so, the second more detailed consideration was whether the filing date of the biosimilar applications were before the expiry of the Market Prohibition Period or even precluded by the filing prohibition. As reported, there is not currently one reference biologic in any

[409] 5 years was chosen as a very conservative benchmark for the assessment period of the biosimilar application filing to potentially overlap with any remaining data exclusivity period.

of Canada, the US and EU where the relevant national data exclusivity provisions were operative in respect of the regulation of the referencing biosimilars.

TABLE 6 – FIRST AUTHORIZATION DATES IN CANADA, THE US AND EU OF REFERENCE BIOLOGICS OF APPROVED BIOSIMILARS IN INDICATED JURISDICTIONS

Reference Biologic	First US FDA Approval	US Data Exclusivity Effect on Biosimilars	First EU EMA Approval	EU Data Exclusivity Effect on Biosimilars	First Canadian HC Approval	Can Data Exclusivity Effect on Biosimilars
AVASTIN (bevacizumab)	2/26/2004	None	1/12/2005	None	9/9/2005	None
ENBREL (etanercept)	11/2/1998	None	2/2/2000	None	12/1/2000	None
EPREX/ERYPO / PROCRIT (epoetin alfa)	6/1/1989	None	1/6/1989	None		
FORSTEO (teriparatide)			6/10/2003	None		
GENOTROPIN (somatropin)			8/3/1988	None	1/19/1998	None
GONAL-F (follitropin alfa)			10/20/1995	None		
HERCEPTIN (trastuzumab)	9/25/1998	None	8/28/2000	None	8/13/1999	None
HUMALOG (insulin lispro)	6/14/1996	None	4/30/1996	None	10/8/1996	None
HUMIRA (adalimumab)			9/8/2003	None	9/24/2004	None
LANTUS (insulin glargine)			6/9/2000	None	4/3/2002	None
LOVENOX (enoxaparin sodium)			Pre-2000	None		
MABTHERA/ RITUXIMAB (rituximab)	11/26/1997	None	2/06/1998	None	3/17/2000	None
NEUPOGEN (filgrastim)	2/20/1991	None	3/1991	None	1/1/1992	None
NEULASTA (pegfilgrastim)	1/31/2002	None	22/08/2002	None	3/12/2004	None
REMICADE (infliximab)	8/24/1998	None	13/08/1999	None	6/6/2001	None

In theory, not yet practice, the imbalance in the data exclusivity regime does not arise from the mere existence of the prohibition preventing the approval of a biosimilar until

the expiry of the Market Prohibition Period. The challenge is in the disproportionally long filing prohibition period which may result in the practical and unwarranted extension of exclusivity beyond expiry of the ultimate data exclusivity period.

In the US, the *Biosimilars Act* dictates a 4 year filing prohibition period,[410] and a nigh-inconceivable 12 year approval prohibition period unjustified by recent investment recovery models.[411] Importantly, there is an 8 year window during which biosimilar applications may be submitted to and assessed by the FDA. This 8 year window provides ample opportunity for a biosimilar application to be ready to launch upon the expiry of the data exclusivity period.

The EU's data exclusivity regime, the most generous globally, prescribes a 10 year approval prohibition period and filing prohibition period of 8 years during which time the EMA is precluded from accepting or reviewing any biosimilar applications for market authorization. Additionally, another 1 year period of protection is available where the reference biologic is approved for a new indication providing significant benefit during the filing prohibition period – this is intended to incentivize continued studies of the already approved biologic.[412]

The assessment window in the EU is much shorter between the filing prohibition and Approval Prohibition (2 years), but the efficiency of the EMA/CHMP's assessment of a biosimilar may not inject as much unintended prejudice into the process. The EMA/CHMP's assessment times of biosimilar applications are more likely to be less than 2 years. In effect, the biosimilar applicant has the first 8 years of the data exclusivity Period in which to rely on the biologics' information and data in the development of the biosimilar, empowered to file the submission which more likely than not will be approved before or soon after the expiry of the approval prohibition period.

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[410] US Public Health Services Act at §351(k)(7)(b).

[411] US Public Health Services Act at §351(k)(7)(a). See supra Section 2.2 and the research of Prasad, Wouters and DiMasi.

[412] This additional year is also available where a drug is transferred from being prescribed to over-the-counter which is highly unlikely for a biologic.

The Canadian filing prohibition and Approval Prohibition periods are, respectively, 6 years and 8 years.[413] Like the EU, the window for Health Canada to assess the biosimilar application approximately 2 years, but unlike the EU, Health Canada's assessments are much more custom and reviewed on a case-by-case basis which leads to variability in assessment times. For instance, some of the regulatory reviews took less than a year while others lasted for more than 2.5 years. Where a biosimilar application is not immediately ready to submit upon the expiry of the filing prohibition period, it is more likely than not that normal regulatory assessment times will result in the undue delay of the biosimilar's market authorization beyond the data exclusivity period.

While this assessment is currently speculative, it is not inconceivable that this now identified issue may come into play sooner rather than later given that the more recently developed biologics will become biosimilar targets within the data exclusivity window.

5.6. Summary of Chapter 5

Chapter 5 is the culmination of this work that gives greater understanding of the impact of how the national implementation of Canada's international obligations are affecting the efficient approval of biosimilars and their accessibility to the Canadian public.

As initially explored, the steadily increasing international obligations have been matched by a mirrored legislative ratcheting up in Canada that in most cases go beyond what is stipulated in the international agreements. There does not seems to be a specific reason why Canada regularly goes beyond its obligations, but two possibilities are political and industry pressures.

The most significant impact on the regulation and legal treatment of biosimilars, however, relate to Canada's patent linkages, the US' patent linkages that are intimately

[413] These provision date back to 2006, but it was clarified in 2017 that data exclusivity extended to biologics and applies to biosimilar applications directed to proceed before Health Canada as New Drug Submissions rather than as Abbreviated New Drug Submissions.

tied in practice to patent litigation in Canada, and the prevalence of patent thickets covering all aspects of a given reference biologic.

One of the most significant obstacles faced by biosimilar developers is the lack of clarity about relevant patents and exclusivity timelines in the US' Purple Book which has a indirect, but significant impact in Canada as a result of the strong coordination of Canadian patent litigation from the US. Absent that information, ascertaining risk is an exercise rife with uncertainty where the patent field is unnecessarily obfuscated. Compelling biologic license holders to disclose the patents they identify as eligible for protection pursuant to the US Biosimilars Act would give some clarity, albeit likely not certainty, about the universe of patents that need to be endured or waited upon before a biosimilar is permitted market access.

Couple this lack of transparency with a higher degree of patent "protection" via patent thickets (which operates more like patent deterrence) and the litigation path becomes mired, the risks of which will not necessarily be outweighed by the potential rewards.

At this point in the biologics/biosimilar world, data exclusivity protections have yet to play a role or even be triggered, but that is not to say that these provisions will never have effect in the context of biosimilar regulation. Casting forward, however, it is conceivable that the short 2 year window where the biosimilar application may be filed prior to the expiry of data exclusivity period precluding market access may represent an unwarranted extension of the biologic's exclusivity.

Ultimately, the interconnectivity of the regulatory assessment of biosimilars, biologic "patent thicket" strategies, data exclusivity idiosyncrasies, litigation realities and patent scope uncertainties all work together to varying effect to delay the market entry of biosimilars in Canada, as well as the US. Importantly, Canada is additionally susceptible to the whims of commercial strategy dictated by what is happening in the US and EU by biologic and biosimilar companies that negotiate the price and availability of critically important drugs through litigation settlement arrangements.

CHAPTER 6. Conclusion

Undoubtedly, the biologics/biosimilars industry is one of the most important and valuable global industries that holds the promise of more effective medical treatments, but these cutting edge treatments are profoundly and prohibitively expensive. However, biologics hold the potential to expand the frontiers of medical treatments for the betterment of Canadian patients and are of particular importance in the development of treatments for chronic and often disabling conditions such as diabetes, autoimmune diseases and cancer, going beyond the capabilities of existing pharmaceutical drugs. Thus, developing and facilitating the development and approval of biosimilars to spur competition will drive prices down[414] for the benefit of patients and payers alike.[415]

Canada's history from the 1920s to 1980s provides an interesting backdrop to the current research; Canada was the home of a burgeoning generic pharmaceuticals industry relying on a "compulsory licensing" model that forced brand pharmaceutical companies to license its patented inventions to generic manufacturers for low and set licensing royalties. This regime was replaced by the first patent linkage regulations in the early 90s which was undoubtedly implemented under the influence of the US, EU and their brand pharmaceutical industries concentrated predominately in the US and EU, as well as Japan and Switzerland, through the international trade agenda. Over time and continued influences, expanded patent and regulatory provisions were mandated by various international treaties, namely data exclusivity and other patent/IP considerations including patent term extensions and *sui generis* rights. It is Canada's domestic implementation of its international treaty obligations that has served to dampen the approval of biosimilars and their launch onto the Canadian market.

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[414] Blackstone & Fuhr, TEMPLE JOURNAL OF SCIENCE, TECHNOLOGY AND ENVIRONMENTAL LAW, (2012).

[415] FRANCIS S. COLLINS, THE LANGUAGE OF LIFE: DNA AND THE REVOLUTION IN PERSONALIZED MEDICINE XXIII-XXIV, 231-35, 237-50 (2010). Francis S. Collins, The Language of Life: DNA and the Revolution in Personalized Medicine (2010), XXIII-XXIV, 231-35, 237-50.

The foundation for this research was set in Chapter 2 where economic, technological and the regulatory context of biologics and biosimilars was explored. This chapter is an overview of the technology related to biologics and biosimilars which, as is subsequently addressed, directly influences the way in which these therapeutic agents are both regulated and patented.

The scope of Canada's international obligations, and their changes over time, was reviewed in detail in Chapter 3. This thorough analysis of the evolution of international treaty obligations related to biologics and biosimilars and the way in which patent linkages, data exclusivity and additional IP protection provisions are approached in Canada. In each of Canada, the US and EU, patent laws are statutory constructs where the patentability assessment is governed by jurisdiction. However, the increase of globalization and trade harmonization efforts has shaped the evolution of IP legislation in many countries over the last few decades through the ever evolving and increasingly widespread adoption of international treaty obligations which have been promulgated through the international trade agenda. This inextricable link between intellectual property and international trade was made in the 1980s; any countries with aspirations of attaining or maintaining membership to the WTO would not be able to avoid the requirements of TRIPs. Thus, Chapter 3 was not only a review of current international agreements, but also a canvass how these obligations have shifted, and stiffened, overtime.

Turning to how these obligations have been implemented, Chapter 4 was an analysis of the national legislation, regulations and policies related to the regulation and patenting of biologics and biosimilars. These treaty obligations mandated, either directly or indirectly, the national adoption of patent linkages, data exclusivity and additional IP provisions, but as established in Chapter 4, the exact implementation of this mandate is at Canada's discretion. A quantitative assessment of biosimilars that have been approved and launched in each respective market concluded this chapter and the data was used as a measure of success in achieving the goal of facilitating the approval of

safe and efficacious biosimilars while also incentivizing further innovation in the analysis and discussion set out in Chapter 5.

The analysis and discussion in Chapter 5 was undertaken with a view to gleaning insight into the factors that influence the authorization of biologics and biosimilars based on each states' different approach to the implementation of their international treaty obligations. In short, Chapter 5 is the culmination of this research that gives greater understanding of the impact of how the national implementation of Canada's international obligations are affecting the efficient approval of biosimilars and their accessibility to the Canadian public.

The steadily increasing international obligations adopted nationally resulted in a legislative ratcheting in Canada that in most cases went beyond what was stipulated in the international agreements. There is no express reasoning why Canada regularly goes beyond its obligations, but one can draw strong inferences from Canada's pattern of being susceptible to political pressure from its first and second largest trading partners and the local representatives of the multinational biopharmaceutical.

However, the most significant impact on the regulation and legal treatment of biosimilars was found to be Canada's patent linkages, the US' patent linkages that are intimately tied in practice to patent litigation in Canada, and the prevalence of patent thickets covering all aspects of a given reference biologic.

The list of obstacles faced by biosimilar applicants is topped with the lack of clarity about relevant patents and exclusivity timelines in the US' Purple Book which has had an indirect, but significant impact in Canada as a result of the strong coordination of Canadian patent litigation from the US. Absent that information, ascertaining risk is an unnecessary, lengthy and expensive endeavour where the patent field is needlessly obfuscated. Compelling biologic license holders to disclose the patents they identify as eligible for protection pursuant to the US Biosimilars Act.

Absent this clarity, further complicated by patent thickets, litigation becomes expensive an expensive endeavour which will not necessarily be justified when weighed against the risks of losing the case and potential access to the market.

At this point in the biologics/biosimilar world, data exclusivity protections have yet to play a role or even be triggered, but that is not to say that these provisions will never have effect in the context of biosimilar regulation. Casting forward, however, it is conceivable that the short 2 year window where the biosimilar application may be filed prior to the expiry of data exclusivity period precluding market access may represent an unwarranted extension of the biologic's exclusivity.

Ultimately, the interconnectivity of the regulatory assessment of biosimilars, biologic "patent thicket" strategies, data exclusivity idiosyncrasies, litigation realities and patent scope uncertainties all work together to varying effect to delay the market entry of biosimilars in Canada, as well as the US. Importantly, Canada is additionally susceptible to the whims of commercial strategy dictated by what is happening in the US and EU by biologic and biosimilar companies that negotiate the price and availability of critically important drugs through litigation settlement arrangements.

There is a delicate tension created by various competing policy goals, namely, encouraging the massive amounts of investments required for the development of innovative biologics, promoting continued innovation beyond the initial biologic development and cultivating competition through the development of biosimilars. These goals will not be equitably achieved without striking an appropriate balance in the patenting of biologics/biosimilars and their regulation.

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APPENDIX 1 – BIOSIMILARS APPROVED BY THE US FOOD & DRUG ADMINISTRATION AND MARKET LAUNCH DATES (IF APPLICABLE)

	Biosimilar†	Biosimilar Applicant†	Reference biologic†	FDA Approval Date†	US Market Launch Date‡
1.	ZARXIO (filgrastim-sndz)	Sandoz Inc.	NEOPOGEN (filgrastim)	3/6/2015	7/3/2015
2.	INFLECTRA (infliximab-dyyb)	CELLTRION, Inc.	REMICADE (infliximab)	4/5/2016	11/30/2016
3.	ERELZI (etanercept-szzs)	Sandoz Inc.	ENBREL (etanercept)	8/30/2016	1/1/2029
4.	AJEVITA (adalimumab-atto)	Amgen Inc.	HUMIRA (adalimumab)	9/23/2016	1/31/2023[416]
5.	RENFLEXIS (infliximab-abda)	Samsung Bioepis Co., Ltd.	REMICADE (infliximab)	4/21/2017	7/24/2017
6.	CYLTEZO (adalimumab-adbm)	Boehringer Ingelheim Pharmaceuticals, Inc.	HUMIRA (adalimumab)	8/25/2017	7/1/2023
7.	MVASI (becavizumab-awwb)	Amgen Inc.	AVASTIN (bevacizumab)	9/14/2017	7/18/2019
8.	IXIFI (infliximab-qbtx)	Pfizer Ireland Pharmaceuticals	REMICADE (infliximab)	12/13/2017	Will never launch[417]
9.	RETACRIT (epoetin alfa-epbx)	Hospira, Inc.	PROCRIT (epoetin alfa)	5/15/2018	11/12/2018
10.	FULPHILA (pegfilgrastim-jmdb)	Mylan Pharmaceuticals Inc.	NEULASTA (pegfilgrastim)	6/4/2018	7/9/2018
11.	NIVESTYM (filgrastim-aafi)	Hospira, Inc.	NEOPOGEN (filgrastim)	7/20/2018	9/24/2018
12.	HYRIMOZ (adalimumab-adaz)	Sandoz Inc.	HUMIRA (adalimumab)	10/30/2018	9/30/2023[418]
13.	UDENYCA (pegfilgrastim-	Coherus BioSciences, Inc.	NEULASTA (pegfilgrastim)	11/2/2018	1/3/2019

[416] Mehr, 49 (2020).
[417] Pfizer's IXIFI biosimilar was a legacy agent developed by Hospira, which Pfizer acquired in 2015. With a marketing agreement already in place with Celltrion for Inflectra, Pfizer decided not to launch IXIFI in the US. Id. at, 45.
[418] Id. at, 49.

	Biosimilar†	Biosimilar Applicant†	Reference biologic†	FDA Approval Date†	US Market Launch Date‡
	cbqv)				
14.	TRUXIMA (rituximab-abbs)	CELLTRION, Inc.	RITUXAN (rituximab)	11/28/2018	11/7/2019
15.	HERZUMA (trastuzumab-pkrb)	CELLTRION, Inc.	HERCEPTIN (trastuzumab)	12/14/2018	3/16/2020
16.	TRAZIMERA (trastuzumab-qyyp)	Pfizer Ireland Pharmaceuticals	HERCEPTIN (trastuzumab)	3/11/2019	2/15/2020
17.	OGIVRI (trastuzumab-dkst)	Mylan Pharmaceuticals Inc.	HERCEPTIN (trastuzumab)	12/1/2017	12/2/2019[419]
18.	ETICOVO (etanercept-ykro)	Samsung Bioepis Co., Ltd.	ENBREL (etanercept)	4/25/2019	1/1/2029
19.	KANJINTI (trastuzumab-anns)	Amgen Inc.	HERCEPTIN (trastuzumab)	6/13/2019	7/18/2019
20.	ZIRABEV (bevacizumab-bvzr)	Pfizer Inc.	AVASTIN (bevacizumab)	6/27/2019	1/13/2020
21.	RUXIENCE (rituximab-pvvr)	Pfizer Ireland Pharmaceuticals	RITUXAN (rituximab)	7/23/2019	1/13/2020
22.	HADLIMA (adalimumab-bwwd)	Samsung Bioepis Co., Ltd.	HUMIRA (adalimumab)	7/23/2019	6/30/2023[420]
23.	ZIEXTENZO (pegfilgrastim-bmez)	Sandoz Inc.	NEULASTA (pegfilgrastim)	11/4/2019	11/15/2019
24.	ABRILADA (adalimumab-afzb)	Pfizer Inc.	HUMIRA (adalimumab)	11/15/2019	11/20/2023
25.	AVSOLA (infliximab-axxq)	Amgen Inc.	REMICADE (infliximab)	12/6/2019	12/12/2019
26.	ONTRUZANT (trastuzumab-dttb)	Samsung Bioepis Co., Ltd.	HERCEPTIN (trastuzumab)	3/20/2020	4/15/2020
27.	NYVEPRIA (pegfilgrastim-apgf)	Hospira Inc.	NEULASTA (pegfilgrastim)	6/10/2020	Not Yet Launched

[419] Delayed launch due to licensing deal with Genentech. Id. at, 41.
[420] Id. at, 49.

	Biosimilar†	Biosimilar Applicant†	Reference biologic†	FDA Approval Date†	US Market Launch Date‡
28.	HULIO (adalimumab-fkjp)	Mylan Pharmaceuticals Inc.	HUMIRA (adalimumab)	7/6/2020	8/1/2023

† All information reported herein has been obtained from The Purple Book accessed electronically.
‡ All information obtained from publicly available sources as referenced in the following Appendix • endnotes.

APPENDIX 2 - BIOSIMILARS APPROVED BY THE EU EUROPEAN MEDICINES AGENCY AND MARKET LAUNCH DATES (IF APPLICABLE)

	Biosimilar	Biosimilar Applicant	Reference Biologic	EMA Approval Date†	EU Market Launch Date‡
1.	ALPHEON (recombinant human interferon alfa-2a)	BioPartners GmbH	ROFERON-A (recombinant human interferon alfa-2a)		Refused 07/20/2006
2.	SOLUMARV (insulin glargine)	Marvel Lifesciences Ltd	LANTUS (insulin glargine)		Refusal - 11/19/2015
3.	OMNITROPE (somatropin)	Sandoz GmbH	GENOTROPIN (somatropin)	12/4/2006	2006
4.	VALTROPIN (somatropin)	BioPartners GmbH	GENOTROPIN (somatropin)	4/24/2006	Withdrawn - 05/10/2012
5.	ABSEAMED (epoetin alfa)	Medice Arzneimittel Pütter GmbH Co. KG	EPREX/ERYPO (epoetin alfa)	8/28/2007	end of 2007
6.	BINOCRIT (epoetin alfa)	Sandoz GmbH	EPREX/ERYPO (epoetin alfa)	8/28/2007	end of 2007
7.	EPOETIN ALFA HEXAL (epoetin alfa)	Hexal AG	EPREX/ERYPO (epoetin alfa)	8/28/2007	
8.	RETACRIT (epoetin alfa)	Pfizer Europe MA EEIG	EPREX/ERYPO (epoetin alfa)	12/18/2007	early 2008
9.	SILAPO (epoetin alfa)	Stada Arzneimittel AG	EPREX/ERYPO (epoetin alfa)	12/18/2007	early 2008 - same article as Retacrit - different trade names
10.	BIOGRASTIM (filgrastim)	AbZ-Pharma GmbH	NEOPOGEN (filgrastim)	9/15/2008	Withdrawn on 09/23/2015
11.	FILGRASTIM RATIOFARM (filgrastim)	Ratiopharm GmbH	NEOPOGEN (filgrastim)	9/15/2008	Withdrawn on 09/15/2009
12.	RATIOGRASTIM (filgrastim)	Ratiopharm GmbH	NEOPOGEN (filgrastim)	9/15/2008	2008
13.	TEVAGRASTIM (filgrastim)	Teva GmbH	NEOPOGEN (filgrastim)	9/15/2008	2009
14.	FILGRASTIM HEXAL (filgrastim)	Hexal AG	NEOPOGEN (filgrastim)	2/6/2009	

	Biosimilar	Biosimilar Applicant	Reference Biologic	EMA Approval Date†	EU Market Launch Date‡
15.	ZARZIO (filgrastim)	Sandoz GmbH	NEOPOGEN (filgrastim)	2/6/2009	2009
16.	NIVESTIM (filgrastim)	Pfizer Europe MA EEIG	NEOPOGEN (filgrastim)	7/6/2010	
17.	INFLECTRA (infliximab)	Pfizer Europe MA EEIG	REMICADE (infliximab)	9/9/2013	2/16/2015
18.	REMSIMA (infliximab)	Celltrion Healthcare Hungary Kft.	REMICADE (infliximab)	10/9/2013	Early 2015
19.	OVALEAP (follitropin alfa)	Theramex Ireland Limited	GONAL-F (follitropin alfa)	9/27/2013	8/1/2016
20.	GRASTOFIL (filgrastim)	Accord Healthcare, SLU	NEOPOGEN (filgrastim)	10/17/2013	2014
21.	BEMFOLA (follitropin alfa)	Gedeon Richter Plc.	GONAL-F (follitropin alfa)	3/26/2014	Second quarter 2014
22.	ABASAGLAR (insulin glargine) (PREVIOUSLY ABASRIA)	Eli Lilly Nederland B.V.	LANTUS (insulin glargine)	9/9/2014	8/26/2015
23.	ACCOFIL (filgrastim)	Accord Healthcare S.L.U.	NEOPOGEN (filgrastim)	9/17/2014	2/27/2015
24.	BENEPALI (etanercept)	Samsung Bioepis NL B.V.	ENBREL (etanercept)	1/13/2016	2/16/2016
25.	FLIXABI (infliximab)	Samsung Bioepis NL B.V.	REMICADE (infliximab)	5/26/2016	9/7/2016
26.	THORINANE (enoxaparin sodium)	Pharmathen S.A.	LOVENOX (enoxaparin sodium)	9/14/2016	Withdrawn 9/15/2019[421]
27.	INHIXA (enoxaparin sodium)	Techdow Pharma Netherlands B.V.	LOVENOX (enoxaparin sodium)	9/15/2016	9/1/2017
28.	TRUXIMA (rituximab)	Celltrion Healthcare Hungary Kft.	MABTHERA (rituximab)	2/17/2017	4/27/2017

[421] Authorization lapsed because it had not been marketed in the EU in the 3 years following authorization

	Biosimilar	Biosimilar Applicant	Reference Biologic	EMA Approval Date†	EU Market Launch Date‡
29.	LUSDUNA (insulin glargine)	Merck Sharp & Dohme B.V.	LANTUS (insulin glargine)	1/3/2017	Withdrawn 10/29/2018
30.	AMGEVITA (adalimumab)	Amgen Europe B.V.	HUMIRA (adalimumab)	3/21/2017	10/16/2018[422]
31.	SOLYMBIC (adalimumab)	Amgen Europe B.V.	HUMIRA (adalimumab)	3/22/2017	withdrawn 06/15/2018
32.	TERROSA (teriparatide)	Gedeon Richter Plc.	FORSTEO (teriparatide)	1/4/2017	8/20/2019
33.	RIXATHON (rituximab)	Sandoz GmbH	MABTHERA (rituximab)	6/15/2017	Prior to October 2019
34.	RIXIMYO (rituximab)	Sandoz GmbH	MABTHERA (rituximab)	6/15/2017	
35.	ERELZI (etanercept)	Sandoz GmbH	ENBREL (etanercept)	6/23/2017	
36.	BLITZIMA (rituximab)	Celltrion Healthcare Hungary Kft.	MABTHERA (rituximab)	7/13/2017	
37.	RITEMVIA (rituximab)	Celltrion Healthcare Hungary Kft.	MABTHERA (rituximab)	7/13/2017	First quarter 2018
38.	RITUZENA (rituximab) (PREVIOUSLY TUXELLA)	Celltrion Healthcare Hungary Kft.	MABTHERA (rituximab)	7/13/2017	Withdrawn 04/10/2019
39.	INSULIN LISPRO SANOFI (insulin lispro)	sanofi-aventis groupe	HUMALOG (insulin lispro)	7/18/2017	Jun-18
40.	IMRALDI (adalimumab)	Samsung Bioepis NL B.V.	HUMIRA (adalimumab)	8/24/2017	10/16/2018
41.	CYLTEZO (adalimumab)	Boehringer Ingelheim International GmbH	HUMIRA (adalimumab)	11/10/2017	Withdrawn 1/15/2019
42.	MOVYMIA (teriparatide)	STADA Arzneimittel AG	FORSTEO (teriparatide)	1/11/2017	Aug-19

[422] Launched upon the expiry of the main European patents. Mehr, 49 (2020).

	Biosimilar	Biosimilar Applicant	Reference Biologic	EMA Approval Date†	EU Market Launch Date‡
43.	ONTRUZANT (trastuzumab)	Samsung Bioepis NL B.V.	HERCEPTIN (trastuzumab)	11/15/2017	3/2018[423]
44.	MVASI (bevacizumab)	Amgen Technology (Ireland) UC	AVASTIN (bevacizumab)	1/15/2018	Avastin retains patent exclusivity until 2022
45.	SEMGLEE (insulin glargine)	Mylan S.A.S	LANTUS (insulin glargine)	3/23/2018	11/14/2018
46.	KANJINTI (trastuzumab)	Amgen Europe B.V.	HERCEPTIN (trastuzumab)	5/16/2018	
47.	ZESSLY (infliximab)	Sandoz GmbH	REMICADE (infliximab)	5/18/2018	Nov-18
48.	HALIMATOZ (adalimumab)	Sandoz GmbH	HUMIRA (adalimumab)	7/26/2018	10/16/2018
49.	HEFIYA (adalimumab)	Sandoz GmbH	HUMIRA (adalimumab)	7/26/2018	Expected October 2018
50.	HYRIMOZ (adalimumab)	Sandoz GmbH	HUMIRA (adalimumab)	7/26/2018	10/16/2018
51.	TRAZIMERA (trastuzumab)	Pfizer Europe MA EEIG	HERCEPTIN (trastuzumab)	7/26/2018	April 1 2019 in Spain
52.	HERZUMA (trastuzumab)	Celltrion Healthcare Hungary Kft.	HERCEPTIN (trastuzumab)	8/02/2018	5/2/2018
53.	HULIO (adalimumab)	Mylan S.A.S.	HUMIRA (adalimumab)	9/16/2018	10/16/2018
54.	PELGRAZ (pegfilgrastim)	Accord Healthcare S.L.U.	NEULASTA (pegfilgrastim)	9/21/2018	
55.	UDENYCA (pegfilgrastim)	ERA Consulting GmbH	NEULASTA (pegfilgrastim)	9/21/2018	Not yet launched
56.	FULPHILA (pegfilgrastim)	Mylan S.A.S	NEULASTA (pegfilgrastim)	11/20/2018	4/28/2020
57.	PELMEG (pegfilgrastim)	Mundipharma Biologics S.L.	NEULASTA (pegfilgrastim)	11/20/2018	2/5/2019
58.	ZIEXTENZO (pegfilgrastim)	Sandoz GmbH	NEULASTA (pegfilgrastim)	11/22/2018	

[423] Id. at, 42.

	Biosimilar	Biosimilar Applicant	Reference Biologic	EMA Approval Date†	EU Market Launch Date‡
59.	OGIVRI (trastuzumab)	Mylan S.A.S	HERCEPTIN (trastuzumab)	12/12/2018	
60.	ZIRABEV (bevacizumab)	Pfizer Europe MA EEIG	AVASTIN (bevacizumab)	2/14/2019	Avastin retains patent exclusivity until 2022
61.	IDACIO (adalimumab)	Fresenius Kabi Deutschland GmbH	HUMIRA (adalimumab)	2/4/2019	5/3/2019
62.	KROMEYA (adalimumab)	Fresenius Kabi Deutschland GmbH	HUMIRA (adalimumab)	2/4/2019	withdrawn 12/17/2019
63.	GRASUSTEK (pegfilgrastim)	Juta Pharma GmbH	NEULASTA (pegfilgrastim)	6/20/2019	
64.	CEGFILA (pegfilgrastim) (PREVIOUSLY PEGFILGRASTIM MUNDIPHARMA)	Mundipharma Corporation (Ireland) Limited	NEULASTA (pegfilgrastim)	12/19/2019	
65.	AMSPARITY (adalimumab)	Pfizer Europe MA EEIG	HUMIRA (adalimumab)	2/13/2020	0/0/0
66.	RUXIENCE (rituximab)	Pfizer Europe MA EEIG	MABTHERA (rituximab)	1/4/2020	Anticipated late 2020
67.	NEPEXTO (etanercept)	Mylan IRE Healthcare Limited	ENBREL (etanercept)	5/20/2020	not yet to market

† All information obtained from EMA accessed electronically.

‡ All information obtained from publicly available sources as referenced in the following Appendix • endnotes.

APPENDIX 3 - BIOSIMILARS APPROVED BY HEALTH CANADA AND MARKET LAUNCH DATES (IF APPLICABLE)

	Biosimilar	Biosimilar Applicant	Reference Biologic	Date Of Market Authorization	Can Market Launch Date
1.	OMNITROPE (somatropin)	Sandoz Canada Incorporated	GENOTROPIN (somatropin)	4/20/2009	4/20/2009
2.	INFLECTRA (infliximab)	Celltrion Healthcare Co Ltd	REMICADE (infliximab)	1/15/2014	9/4/2014
3.	REMSIMA (infliximab) (MARKETED AS INFLECTRA)	Celltrion Healthcare Co Ltd	REMICADE (infliximab)	1/15/2014	9/18/2014
4.	BASAGLAR (insulin glargine)	Eli Lilly Canada Inc	LANTUS (insulin glargine)	9/1/2015	12/18/2015
5.	GRASTOFIL (filgrastim)	Apotex Inc	NEOPOGEN (filgrastim)	12/7/2015	3/17/2016
6.	BRENZYS (etanercept)	Samsung Bioepis Co., Ltd	ENBREL (etanercept)	5/31/2016	9/23/2016
7.	ERELZI (etanercept)	Sandoz Canada Incorporated	ENBREL (etanercept)	4/6/2017	8/4/2017
8.	ADMELOG (insulin lispro)	Sanofi-Aventis Canada Inc	HUMALOG (insulin lispro)	11/16/2017	11/22/2019
9.	RENFLEXIS (infliximab)	Samsung Bioepis Co., Ltd	REMICADE (infliximab)	12/1/2017	3/22/2018
10.	LAPELGA (pegfilgrastim)	Apotex Inc	NEULASTA (pegfilgrastim)	4/5/2018	2/27/2019
11.	MVASI (bevacizumab)	Amgen Canada Inc	AVASTIN (bevacizumab)	4/30/2018	8/1/2019
12.	HADLIMA (adalimumab)	Samsung Bioepis Co., Ltd	HUMIRA (adalimumab)	5/8/2018	
13.	FULPHILA (pegfilgrastim)	BGP Pharma Ulc	NEULASTA (pegfilgrastim)	12/24/2018	2/7/2020
14.	TRUXIMA (rituximab)	Celltrion Healthcare Co Ltd	RITUXAN (rituximab)	4/4/2019	12/11/2019
15.	OGIVRI (trastuzumab)	BGP Pharma Ulc	HERCEPTIN (trastuzumab)	5/3/2019	6/6/2019

	Biosimilar	Biosimilar Applicant	Reference Biologic	Date Of Market Authorization	Can Market Launch Date
16.	ZIRABEV (bevacizumab)	Pfizer Canada Ulc	AVASTIN (bevacizumab)	6/14/2019	9/25/2019
17.	TRAZIMERA (trastuzumab)	Pfizer Canada Ulc	HERCEPTIN (trastuzumab)	8/15/2019	10/22/2019
18.	HERZUMA (trastuzumab)	Celltrion Healthcare Co Ltd	HERCEPTIN (trastuzumab)	9/3/2019	12/11/2019
19.	KANJINTI (trastuzumab)	Amgen Canada Inc	HERCEPTIN (trastuzumab)	2/27/2020	4/16/2020
20.	AVSOLA (infliximab)	Amgen Canada Inc	REMICADE (infliximab)	3/12/2020	6/1/2020
21.	NIVESTYM (filgrastim)	Pfizer Canada Ulc	NEOPOGEN (filgrastim)	4/16/2020	5/11/2020
22.	ZIEXTENZO (pegfilgrastim)	Sandoz Canada Incorporated	NEULASTA (pegfilgrastim)	4/21/2020	6/15/2020
23.	RIXIMYO (rituximab)	Sandoz Canada Incorporated	RITUXAN (rituximab)	4/28/2020	
24.	RUXIENCE (rituximab)	Pfizer Canada Ulc	RITUXAN (rituximab)	5/4/2020	5/26/2020

† All information obtained from Health Canada • accessed electronically.
‡ All information obtained from Health Canada's • accessed electronically.

APPENDIX 4 – COMPARISON OF BIOSIMILAR APPROVALS AND MARKET LAUNCH DATES IN THE EU, US AND CANADA

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
	HUMIRA (adalimumab)	9/8/2003				9/24/2004	
1.	AMGEVITA (adalimumab) (AJEVITA in the US)	3/21/2017	10/16/2018	9/23/2016	1/31/2023		
2.	IMRALDI (adalimumab) (HADLIMA in US and Canada	8/24/2017	10/16/2018	7/23/2019	6/30/2023	5/8/2018	
3.	CYLTEZO (adalimumab)	11/10/2017	Withdrawn 1/15/2019	8/25/2017	7/1/2023		
4.	HALIMATOZ (adalimumab)	7/26/2018	10/16/2018				
5.	HEFIYA (adalimumab)	7/26/2018	Expected October 2018				
6.	HYRIMOZ (adalimumab)	7/26/2018	10/16/2018	10/30/2018	9/30/2023		
7.	HULIO (adalimumab)	9/16/2018	10/16/2018	7/6/2020	8/1/2023		
8.	IDACIO (adalimumab)	2/4/2019	5/3/2019				
9.	AMSPARITY (adalimumab) (ABRILADA in the US)	2/13//2020	0/0/0	11/15/2019	11/20/2023		
	HERCEPTIN (trastuzumab)	8/28/2000		9/25/1998		8/13/1999	
10.	ONTRUZANT (trastuzumab)	11/15/2017	3/2018	3/20/2020	4/15/2020		
11.	HERZUMA (trastuzumab)	2/8/2018	5/2/2018	12/14/2018	3/16/2020	9/3/2019	12/11/2019
12.	KANJINTI (trastuzumab)	5/16/2018		6/13/2019	7/18/2019	2/27/2020	4/16/2020

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
13.	TRAZIMERA (trastuzumab)	7/26/2018	April 1 2019 in Spain	3/11/2019	2/15/2020	8/15/2019	10/22/2019
14.	OGIVRI (trastuzumab)	12/12/2018		12/1/2017	12/2/2019	5/3/2019	6/6/2019
	AVASTIN (bevacizumab)	1/12/2005		2/26/2004		9/9/2005	
15.	MVASI (bevacizumab)	1/15/2018	Avastin retains patent exclusivity until 2022	11/16/2017	11/22/2019	4/30/2018	8/1/2019
16.	ZIRABEV (bevacizumab)	2/14/2019	Avastin retains patent exclusivity until 2022	6/27/2019	1/13/2020	6/14/2019	9/25/2019
	ENBREL (etanercept)	2/2/2000		11/2/1998		12/1/2000	
17.	BENEPALI (etanercept) (BRENZYS in Canada; ETICOVO in the US)	1/13/2016	2/16/2016	4/25/2019	1/1/2029	5/31/2016	9/23/2016
18.	ERELZI (etanercept)	6/23/2017		8/30/2016	1/1/2029	4/6/2017	8/4/2017
19.	NEPEXTO (etanercept)	5/20/2020	not yet to market				
	EPREX/ERYPO / PROCRIT (epoetin alfa)	1/6/1989		6/1/1989			
20.	ABSEAMED (epoetin alfa)	8/28/2007	End of 2007				
21.	BINOCRIT (epoetin alfa)	8/28/2007	End of 2007				
22.	EPOETIN ALFA HEXAL (epoetin alfa)	8/28/2007					

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
23.	RETACRIT (epoetin alfa)	12/18/2007	Early 2008	5/15/2018	11/12/2018		
24.	SILAPO (epoetin alfa)	12/18/2007	Early 2008 - same article as Retacrit - different trade names				
	FORSTEO (teriparatide)	6/10/2003					
25.	TERROSA (teriparatide)	1/4/2017	8/20/2019				
26.	MOVYMIA (teriparatide)	1/11/2017	8/2019				
	GENOTROPIN (somatropin)	8/3/1988				1/19/1998	
27.	OMNITROPE (somatropin)	12/4/2006	2006			4/20/2009	4/20/2009
	GONAL-F (follitropin alfa)	10/20/1995					
28.	OVALEAP (follitropin alfa)	9/27/2013	8/1/2016				
29.	BEMFOLA (follitropin alfa)	3/26/2014	Q2 2014				
	HUMALOG (insulin lispro)	4/30/1996		6/14/1996		10/8/1996	
30.	INSULIN LISPRO SANOFI (insulin lispro) (ADMELOG in Canada)	7/18/2017	6/2018			11/16/2017	11/22/2019
	LANTUS (insulin glargine)	6/9/2000				4/3/2002	
31.	ABASAGLAR (insulin glargine) (PREVIOUSLY	9/9/2014	8/26/2015			9/1/2015	12/18/2015

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
	ABASRIA) (BASAGLAR in Canada)						
32.	SEMGLEE (insulin glargine)	3/23/2018	11/14/2018				
	LOVENOX (enoxaparin sodium)	Pre-2000					
33.	INHIXA (enoxaparin sodium)	9/15/2016	9/1/2017				
	MABTHERA/ RITUXIMAB (rituximab)	2/06/1998		11/26/1997		3/17/2000	
34.	TRUXIMA (rituximab)	2/17/2017	4/27/2017	11/28/2018	11/7/2019	4/4/2019	12/11/2019
35.	RIXATHON (rituximab)	6/15/2017	Prior to October 2019				
36.	RIXIMYO (rituximab)	6/15/2017				4/28/2020	
37.	BLITZIMA (rituximab)	7/13/2017					
38.	RITEMVIA (rituximab)	7/13/2017	Q1 2018				
39.	RUXIENCE (rituximab)	1/4/2020	Anticipated late 2020	7/23/2019	1/13/2020	5/4/2020	5/26/2020
	NEUPOGEN (filgrastim)	3/1991		2/20/1991		1/1/1992	
40.	RATIOGRASTIM (filgrastim)	9/15/2008	2008				
41.	TEVAGRASTIM (filgrastim)	9/15/2008	2009				
42.	FILGRASTIM HEXAL (filgrastim)	2/6/2009					
43.	ZARZIO (filgrastim) (ZARXIO in the US)	2/6/2009	2009	3/6/2015	7/3/2015		

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
44.	NIVESTIM (filgrastim) (NIVESTYM in the US and Canada)	7/6/2010		7/20/2018	9/24/2018	4/16/2020	5/11/2020
45.	GRASTOFIL (filgrastim)	10/17/2013	2014			12/7/2015	3/17/2016
46.	ACCOFIL (filgrastim)	9/17/2014	2/27/2015				
	NEULASTA (pegfilgrastim)	22/08/2002		1/31/2002		3/12/2004	
47.	LAPELGA (pegfilgrastim)					4/5/2018	2/27/2019
48.	PELGRAZ (pegfilgrastim)	9/21/2018					
49.	UDENYCA (pegfilgrastim)	9/21/2018	Not yet launched	11/2/2018	1/3/2019		
50.	FULPHILA (pegfilgrastim)	11/20/2018	4/28/2020	6/4/2018	7/9/2018	12/24/2018	2/7/2020
51.	PELMEG (pegfilgrastim)	11/20/2018	2/5/2019				
52.	ZIEXTENZO (pegfilgrastim)	11/22/2018		11/4/2019	11/15/2019	4/21/2020	6/15/2020
53.	NYVEPRIA (pegfilgrastim-apgf)			6/10/2020	Not Yet Launched		
54.	GRASUSTEK (pegfilgrastim)	6/20/2019					
55.	CEGFILA (pegfilgrastim) (PREVIOUSLY PEGFILGRASTIM MUNDIPHARMA)	12/19/2019					
	REMICADE (infliximab)	13/08/1999		8/24/1998		6/6/2001	
56.	INFLECTRA (infliximab)	9/9/2013	2/16/2015	4/5/2016	11/30/2016	1/15/2014	9/4/2014
57.	REMSIMA	9/10/2013	Early 2015			1/15/2014	9/18/2014

	Biosimilar	EMA Approval Date	Marketing Launch Date	US Approval Date	US Market Launch Date	Canadian Approval Date	Canadian Launch Date
	(infliximab)						
58.	FLIXABI (infliximab) (RENFLEXIS in the US and Canada)	5/26/2016	9/7/2016	4/21/2017	7/24/2016	12/1/2017	3/22/2018
59.	ZESSLY (infliximab)	5/18/2018	Nov-18				
60.	AVSOLA (infliximab)[424]			12/6/2019	12/12/2019	3/12/2020	6/1/2020

[424] Application before the EMA withdrawn due to a change in product strategy. Amgen Limited, AVSOLA EU Withdrawal Amgen Letter (2019).