Health Policy 123 (2019) 1251–1258

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

How will recent trade agreements that extend market protections for brand-name prescription pharmaceuticals impact expenditures and generic access in Canada?

Reed F. Beall[a,*], Lorian Hardcastle[a,b], Fiona Clement[a], Aidan Hollis[c]

[a] Cummings School of Medicine and O'Brien Institute of Public Health, University of Calgary, Calgary, AB, Canada
[b] Faculty of Law, University of Calgary, Calgary, AB, Canada
[c] Department of Economics, University of Calgary, Calgary, AB, Canada

ARTICLE INFO

Article history:
Received 12 June 2019
Received in revised form 9 September 2019
Accepted 14 September 2019

Keywords:
Pharmaceutical policy
Globalization and health
Health care reform
Drug pricing
Health spending
International trade
Patents
Data exclusivities
Health law

ABSTRACT

Canada recently entered into two multinational trade agreements (i.e., the Canada, United States, and Mexico Trade Agreement; and the Comprehensive Economic and Trade Agreement with the European Union). The resulting federal policy changes will prolong periods of market protection afforded to eligible brand-name prescription drugs by extending competition-blocking patent and data exclusivity terms. While previous studies have analysed these two policy changes in isolation, it remains unknown what the total combined impact will be in a typical year. Our objective was to design an analytic approach that can assess more than one change to a country's market protections and then to apply this methodology to the Canadian context. We find that the collective impact of these policy changes will be to extend the regulatory protection period for new drugs from an average of 10.0 years to 11.1 years. Depending upon the model's assumptions and all contingencies considered, an 11% increase equated to an average of $410 million annually (with a minimum estimate of $40 million and a maximum of $1.4 billion). Despite this uncertainty reflected in the range of possible financial impacts, we conclude that such methodological approaches could be useful for rapidly evaluating potential policy changes prior to adoption, which may further assist in budget planning to mitigate increased cost to the downstream health authorities most impacted by these trade concessions.

1. Introduction

As a result of two multinational trade agreements, Canada recently amended federal patent regulations to prolong periods of market protection afforded to new brand name prescription drugs in order to be more closely aligned with policies in peer countries [1]. As these periods of protection prevent lower-cost generic competition from market entry, these changes may have implications for drug expenditures and access.

As a result of Canada's trade agreement with the European Union, the Comprehensive Economic and Trade Agreement (CETA), patents associated with drugs products containing new medicinal ingredients (or combinations of ingredients) never before approved by Health Canada will be extended by up to two years [2,3]. Extending patent protection prolongs the time in which brand name manufacturers may charge the highest allowable prices for their products in the absence of competition.

The second deal was part of the renegotiation of the Canada, United States, Mexico Trade Agreement (also known as "CUSMA" and previously as "NAFTA"). CUSMA will extend data exclusivities for biologic drugs (i.e., a specific type of pharmaceutical product now representing nearly one-half of all new drugs approved by Health Canada each year) (Textbox 1) from 8 years to 10 years [1]. Data exclusivities bar Health Canada from approving applications from generic competitors that seek to demonstrate safety and efficacy by referencing the clinical trial data provided in the brand name manufacturer's application for regulatory approval.

Previous studies have sought to evaluate the potential impact of patent term extensions and of extending biologic exclusivities [3–5]; however, it remains unknown what the total combined impact will be in a typical year, particularly considering that many new drugs are often protected by multiple patents expiring at different times, which may outlast both extended patents and data exclusivities. Canada's need to evaluate the impact of multiple

* Corresponding author at: 3280 Hospital Drive NW, Calgary, AB T2N 4Z6, Canada.
E-mail address: Reed.Beall@ucalgary.ca (R.F. Beall).

https://doi.org/10.1016/j.healthpol.2019.09.005
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Table 1
Estimated financial impact of extended regulatory protections in Canada assuming $16.8 billion in annual expenditures on patented medicines.

Assumptions	Number of other suppliers		
	1 competitor (25% cost reduction)	2 competitors (50% cost reduction)	3 or more competitors (75% cost reduction)
All drugs experience entry of competition when last regulatory protection expires	$462 million	$924 million	$1.4 billion
52% of drugs experience entry of competition when last regulatory protection expires	$240 million	$480 million	$721 million
All drugs experience entry of competition when last regulatory protection expires or 12.3 years have elapsed, whichever is more	$77 million	$154 million	$231 million
52% of drugs experience entry of competition when last regulatory protection expires or 12.3 years have elapsed, whichever is more	$40 million	$80 million	$120 million

Estimated increased spending under various assumptions due to prolonged exclusivity periods for biologics and the introduction of Certification of Supplementary Protection (CSP) for all patented medications. The assumptions are based upon a recent study which found that of the 52% of top-selling drugs that experienced generic entry during the observation period, the average duration of the competition-free period was 12.3 years [29]. The most conservative cost estimates assume that both of these observations will hold true in the future, meaning that only CSPs will effectually prolong the competition-free period beyond 12.3 years. The spending reductions due to the number of generic suppliers are based upon the Pan-Canadian Generics' pricing framework [24]. Total expenditure on patented medicines ($16.8 billion) is the most-recently reported by the Patented Medicines Review Board Report [23]. While which of the above estimates is most justified is a matter of considered opinion based upon what will be most accurate to reality in the future when these regulatory protections expire, an average ($410 million) or median point estimate ($235 million) may prove most reliable. Note, that the lost opportunity for savings estimated for small molecule drugs is likely higher than for biologics given that more small-molecule drugs receive generic competition after patents expire (triggering automatic substitution laws) whereas biologics rarely receive biosimilar competition, but these dynamics may change in the future.

changes to market protections for brand-name drugs is not unique [6–8]. The objective of this empirical legal study is to develop an analytic approach that can evaluate the implications of multiple changes to market protection terms for brand-name drugs and apply the methodology to the Canadian context. The approach involves mapping the regulatory landscape before and after recent amendments to market protections for new drugs (i.e., the time during which Health Canada cannot approve applications from generic competitors due to data exclusivity or patent protection listed in its register) and then estimating the potential financial implications of adopting those new policies relative to status quo.

2. Background

2.1. Competition-free periods: drug innovation's financial incentive

When a new drug is introduced to the market, there is a limited period of time in which that drug innovator has access to a competition-free market (See Textbox 1 for common definitions of terms). During this time, manufacturers may charge the highest price that the market will bear, within the limits set by the Patented Medicines Prices Review Board, in order to make a profit and recuperate commercial investment. There are two distinct types of market protection that implicate Health Canada, namely, (i) patent protection and (ii) data exclusivity. As both forms of market protection often run in parallel, most new drugs are doubly protected from competition upon market launch (throughout this article, we refer to these two mechanisms collectively as "regulatory market protections") (Fig. 1).

2.1.1. Patents and patent term extensions as a form of market protection

Since 1989, patents have been granted by the Canadian Intellectual Property Office (CIPO) for a standard period of 20 years from the time of application. In order for a proposed invention to be patentable, the Patent Act specifies three criteria, namely, that the proposed invention be (i) novel (i.e., does not already exist in society), (ii) non-obvious (i.e., it makes an inventive step that would not be obvious to other experts in the field), and (iii) useful (e.g., it has commercial applications and can generate new industries). Patent protections give the patent holder the prerogative to attempt to seek compensation from those who have infringed upon their intellectual property during the patent term. That said, patents' validity and relevance can be challenged in court.

Patents associated with a pharmaceutical product may be submitted by drug manufacturers to Health Canada for listing in their register (note that patents covering manufacturing processes or delivery devices are not eligible for listing). Health Canada cannot approve applications for market entry from generic equivalents when patents for the brand name product are listed in the register, unless it has first notified the brand name manufacturer and either the brand name manufacturer elected not to pursue litigation, patent litigation has been resolved, or 24 months has elapsed (called the 'statutory stay'). Thus, listed patents can postpone regulatory approvals for generic and biosimilar manufacturers. Unlisted patents can discourage generic manufacturers from entering a market, but they cannot formally interfere with or delay Health Canada approvals [9].

As patents are often filed early in the drug development process and prior to clinical testing in humans, much of the patent term is expended before the drug has been approved and can be marketed. A recent study found that pharmaceutical patents were filed a median of 12.3 years (IQR: 9.4–15.1) prior to gaining marketing approval in the United States (as measured by the first patent filing globally to approval by the US Food and Drug Administration) [10]. To compensate for this patent time lost, some countries provide a patent term extension [11]. Canada had no such patent term extension policy until CETA.

On 21 September 2017, CIPO in cooperation with Health Canada began to issue Certificates of Supplementary Protection (CSP) to extend patents on pharmaceuticals. Only products containing new active ingredients or combinations of active ingredients that have never before been approved in Canada are eligible. The product in question must be introduced in Canada within 12 months of approval in peer countries (the EU, US, Australia, Switzerland, and Japan). The exact extension term is calculated using the following formula: the date of Health Canada approval (Notice of Compli-

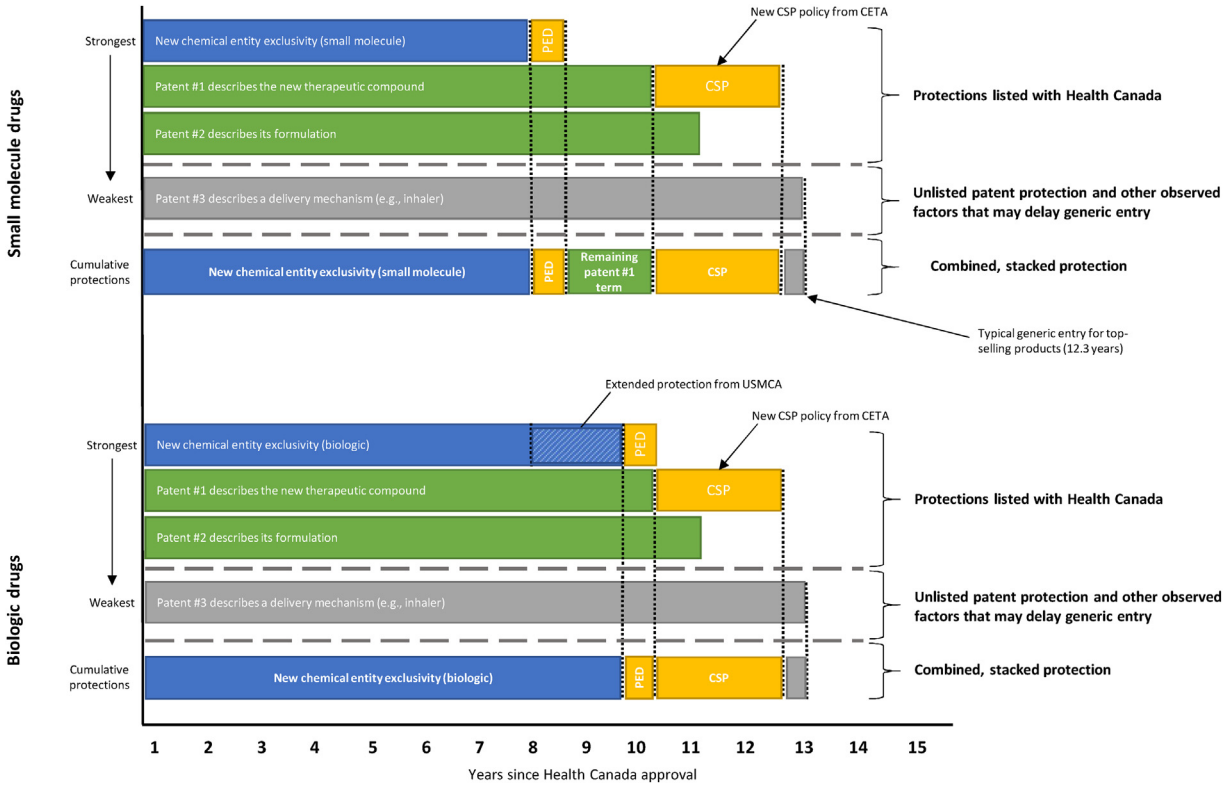

Fig. 1. Summary of overlapping layers of market protections for the average drug containing a new active substance and their respective expirations.
The typical drug containing a new active substance is approved in Canada with multiple market protections, which vary in their proven ability to ensure a competition-free marketplace for a limited period of time. The strongest market protections are those which cannot be challenged or called into question and that bar Health Canada from approving applications from generic or biosimilar competitors whose products' safety and efficacy are based upon its equivalence with the original, brand-name version of the drug testing in clinical trials. These data exclusivities can be extended by 6-months when clinical testing has been conducted to ensure safety and efficacy in pediatric populations. Patents that have been listed in Health Canada's patent register are the next strongest form of market protection because patent linkage applies, meaning that Health Canada cannot approve a biosimilar or generic equivalent until the patent expires, until patent litigation has been resolved, or until 24-months has elapsed. Patents extended by CSP have been shown to be relatively good predictor of generic entry because manufacturers often choose to extend a patent that protects the active ingredient itself, rather than other aspects of the medicines purported to be a new active substance, such as the products' formulation (e.g., an oral tablet or solution for injection as the method of administration) or its delivery device.

ance) is subtracted from the date of the patent application filing in Canada minus 5 years. The extension terms may not exceed 2 years [12].

2.1.2. Data exclusivity as a form of market protection

The second form of market protection is data exclusivity. Data exclusivities bar regulatory authorities like Health Canada from approving an application[1] for market entry from a direct competitor, such as a generic drug manufacturer, whose clinical evidence for safety and efficacy is reliant upon the brand name manufacturer's studies. Currently, all pharmaceutical products containing a novel medicinal ingredient (i.e., an active ingredient that has never before been approved by Health Canada) receive 8 years of exclusivity. However, due to the new CUSMA agreement, biologic drugs will soon receive an additional 2 years (i.e., 10 years total) of data exclusivity. Note that drugs containing a new active substance with clinical data on use in pediatric populations are eligible for an additional six-month exclusivity, which is added to the end of the original data exclusivity period; thus, new drugs with additional testing in pediatric populations may receive a total of 8.5 and 10.5 years of data protection for small molecule or biologic drugs respectively [13].

2.2. The relative strength of these two overlapping forms of market protections

While both patents and data exclusivities restrict regulatory authorities' ability to approve applications from direct competitors to enter the market, they are not regarded as equivalent mechanisms. Data exclusivities are highly prized by drug developers because, unlike patents, these market protections cannot be challenged by competitors. Data exclusivities, however, often expire before patent protections, depending upon when the patent was originally filed and whether an extension had been granted. In contrast, the validity of patents can be challenged, offering less certain market protection and potential litigation costs.

Patents, however, can outlast data exclusivities, especially when a single product is associated with multiple patents which cover different aspects of the medicine with staggered expiration dates (for example, the patent disclosing the active ingredient's chemical structure is often filed several years before the patent disclosing the manufacturing process). Patents on the substance or chemical structure of a new therapeutic moiety have proven to be more effective at blocking generic competition [14,15] because other

[1] Note that regulatory laws for drugs containing new active ingredients often distinguish between a period when the regulatory authority is barred from beginning the review of applications from generic manufacturers and a period when the regulatory authority may begin issuing approvals for market entry. In Canada, there is technically a 6-year "no file" period within the 8-year "market exclusivity period"; however, in this article, we have adopted the language used by Health Canada's Register of Innovative Drugs and refer to the expiration of the entire 8-year period, plus the pediatric exclusivity where relevant, as the end of the data protection. Note that the draft CUSMA agreement does not propose to alter the 6-year "no file" period for biologics. It will remain the same for both drug types.

patents can be circumvented; for example, a generic manufacturer can use a different manufacturing process to derive an identical active ingredient. Previous research has found that manufacturers typically extend the patent that will be most effective at blocking generic competition and that other later-expiring patents offer far less certain market protection [11,16].

In sum, the ability of these market protections to block competition may be considered to have the following order of strength (from strongest to weakest): data exclusivity (which may be extended by a 6-month pediatric exclusivity), the active ingredient patent and/or the patent selected for extension, other patents listed in the Health Canada's register, and finally, all other patents that are not listed in Health Canada's register. Given that the changes ushered in by CETA and CUSMA will only prolong two of the strongest forms of market protection for some drugs, it is unclear how much longer the average new drug's market protections will be and what the potential financial impact will be.

3. Methods

The first step of our methodological approach was to collect data for mapping the current landscape of market protections for brand name drugs in Canada. We extracted all data available currently from Health Canada's register of Certificate of Supplementary Protection (CSPs) [17], of patents [18], of data exclusivities for drugs containing new active substance [19], of new drug approvals (Notice of Compliance database) [20], and of all approved drug products by Health Canada (Drug Product Database) [21]. While recent studies have found that only 10–15% of the new active substances introduced into the Canadian market are significant therapeutic advances [22], we nonetheless focused upon these drugs as they tend to represent more substantial clinical advances as compared to drugs containing new formulations of existing drugs.

Next, for all drugs containing a new active substance approved in Canada since 21 September 2017 to the time of study (21 March 2019), we calculated products' respective last-expiring patent with and without CSP while taking into account the expiration of the 8-year data exclusivity (plus an additional 6-months of pediatric exclusivity where relevant). To evaluate the potential impact of extending exclusivity for biologics, we conducted a hypothetical simulation in which all biologics products in our study received 10 years of data protection (plus an additional 6-months of pediatric exclusivity where relevant) rather than 8 years. We report on the proportion and number of drugs containing a new active substance to be impacted by these policies. In line with other previous studies [10,11,16], our analysis assumes the previously described order of market protection strength for the respective components of the regulatory protection periods (where relevant): innovative drug data exclusivity (i.e., a drug containing a new active substance), pediatric exclusivity, original patent protection (i.e., the original expiration date of the extended patent), the CSP, and other registered patent protection. We then calculated the amount of time that each form of protection (ranked from strongest to weakest) extended the period of protection beyond the one proceeding it. We report results by average in order to reflect the respective contribution of each mechanism to the overall regulatory protection period. We report on drugs with a CSP separately and then upon all new drugs collectively (including products with and without CSP extensions) for the following scenarios: (i) the regulatory protection period prior to CSP; (ii) the regulatory protection period with the addition of CSP; and finally, (iii) the regulatory protection period with CSP and a 10-year data exclusivity period for biologics.

Finally, to estimate the financial impact, we multiplied the percent change in the regulatory protection period by the most recent available data on national expenditures on patented prescription drugs ($16.8 billion [23]) and by the 25%, 50%, 75% cost fixed price reductions depending upon whether there are one, two, or three or more manufacturers in the market [24]. We note that historically, biosimilar competition in Canada has resulted in relatively modest savings. However, British Columbia recently announced a much more aggressive approach to biosimilars, with mandatory substitution to certain biosimilars [25,26]. If other provinces follow, this will result in much larger price reductions and savings following biosimilar entry.

Our estimates assume that generic entry always occurs immediately upon expiration of regulatory protections, which does not address the possibility of other unobserved factors (e.g., unlisted later-expiring patents [27]) further delaying generic entry. Indeed, Health Canada has advised that the expiration of regulatory protection is not always a good indicator of when a generic will become available [28]. To address these concerns, (i) associated expenditures were calculated if only 52% of drugs experienced generic entry upon expiration of the regulatory protections, and (ii) associated expenditures were calculated only for CSPs that extended patent protections beyond 12.3 years. These thresholds (i.e., 52%, 12.3 years) were used because a recent study on top-selling, novel drugs found that generic competition entered the market an average of 12.3 years after Health Canada approval, a result which aligns with several other studies on the typical timing of generic entry in other jurisdictions [29–31]. This same study found that only 52% of drugs experienced generic entry within its observation period (14.7 years). After calculating the results from all scenarios, we report the average as a middle point estimate which takes into account all contingencies evaluated.

4. Results

Between 21 September 2017 and 21 March 2019, Health Canada approved 59 new active substances that contained an active ingredient never before approved for human use by that regulatory body. These products covered 10 of the WHO's broadest therapeutic categories (i.e., the broadest level of the Anatomical Therapeutic Chemical (ATC) Classification System [32]), with the bulk pertaining to cancer and immunomodulating agents (18/59, 31%); anti-infectives for systemic use (10/59, 17%); and products to treat blood disorders (7/59, 12%).

4.1. The relative impact of CSP on the regulatory protection period

Of the 59 products, 47 (80%) had one or more patents listed in Health Canada's patent register. A CSP application had been filed for 27 of these products, representing 57% (27/47) of all products with listed patent protections and 46% (27/59) of all new active substances (web appendix). While a decision was pending upon 4 of these CSP applications, 19 applications had been granted (4 applications had been refused), reflecting an 83% success rate among applications with decisions. Of the 19 granted CSPs, 16 (84%) were for the full 2-year period. The remaining three terms were 1.9, 1.7, and 0.1 years.

For the subset of 19 drugs that earned a CSP, the total period of regulatory protection increased from an average of 10.9 years (median: 10.8; interquartile range [IQR]: 8.9–12.2) to 12.6 years (median: 12.8; IQR: 10.9–14.2). The CSPs pushed patent protection beyond 12.3 years after Health Canada approval for 11 of 19 drugs (58%); 5 of 19 drugs (26%) were even beyond 14 years. The CSP period now contributes an average of 17% (or 1.7 years) of the overall exclusivity period for this subset of drugs (Fig. 2).

With respect to the impact for the entire cohort of 59 new drugs, the addition of CSP brought the average total period of protection

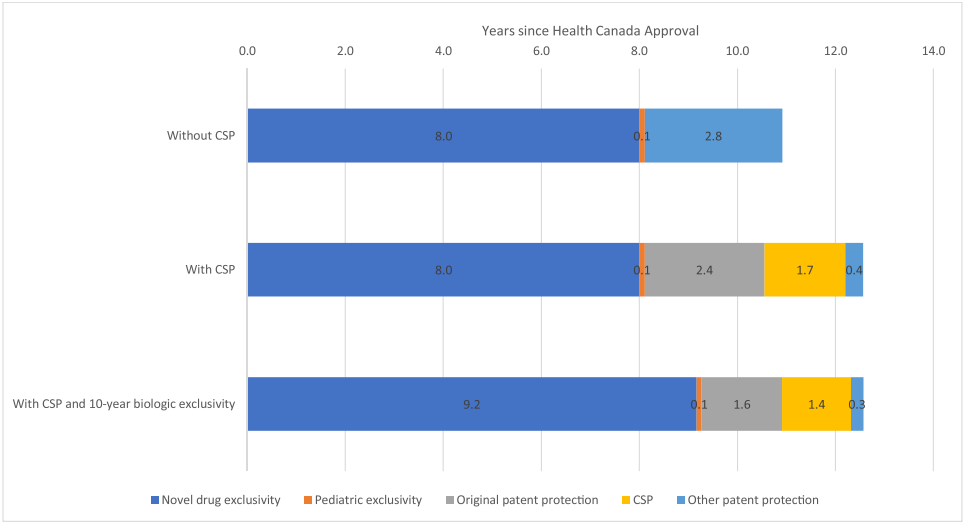

Fig. 2. Breakdown of average segments regulatory market protections for drugs containing a new active substance granted a CSP (n = 19).
Average time segments (in order of strength) within the regulatory protection period for the 19 novel drugs receiving CSPs are shown for the following three scenarios: (i) prior to the addition of CSP, (ii) after the addition of CSP, and (iii) after the addition of CSP if data exclusivity expirations were set to expire after 10 years, rather than 8 years. After the expiration of the novel drug data exclusivity, some drugs receive an additional 6-month (0.5 year) pediatric exclusivity. An extended patents' term typically expires next, followed by the CSP period. On rare occasions, other listed patent protection will expire even later than the patent term extension, marking the end of the regulatory protection period. Unlisted patents may expire even later; indeed, recent evidence has found that generic entry for top-selling drugs often occurs 12.3 years after Health Canada approval.

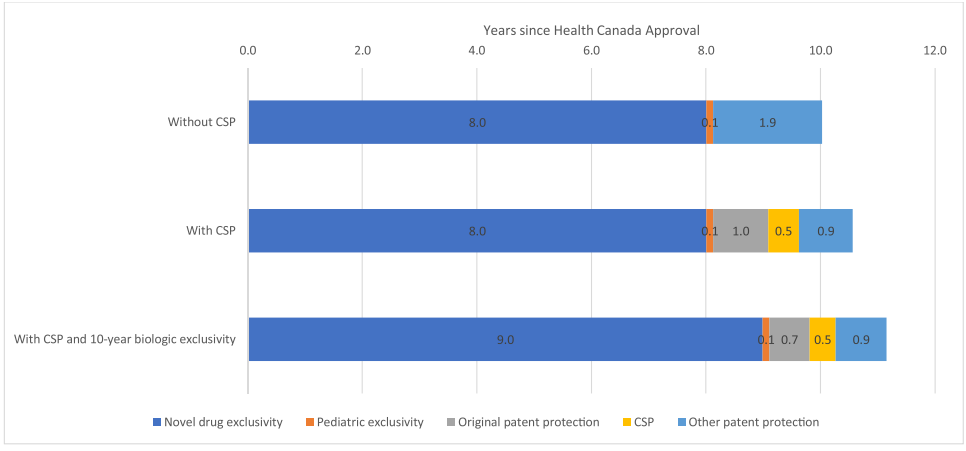

Fig. 3. Breakdown of regulatory protection for drugs containing a new active substance approved since 21 September 2017 (n = 59).
Average time segments (in order of strength) within the exclusivity period for the 59 novel drugs approved during the study period are shown for the following three scenarios: (i) prior to the addition of CSP, (ii) after the addition of CSP, and (iii) after the addition of CSP if data exclusivity expirations were set to expire after 10 years, rather than 8 years.

from 10.0 years (median: 8.5; IQR: 8.0–11.4) to 10.6 years (median: 9.2; IQR: 8.0–12.7) with CSP representing an average of 5% or 7.2 months of this time (Fig. 3).

4.2. The relative impact of a 10-year data protection for biologics on the regulatory protection period

Of the 59 products in the overall cohort, 29 (49%) were biologic drugs. Of these 29, extending data protection would prolong the regulatory protection period for 18 (62%). 10 products had no listed patent protection and another 8 products had patent protections (including CSPs) expiring sooner than 10 years after gaining regulatory approval. The remaining 11 biologic drugs have listed patent protections expiring after the extended data exclusivities, 5 of which were due to CSPs.

The regulatory protection period for the subset of 29 biologic drugs would move from an average of 10.2 years (median: 8.5; IQR: 8.0–12.2) to 11.3 years (median: 10.5; IQR: 10.0–12.2), thereby surpassing the average protection period for the subset of 30 small molecule drugs from the same cohort (average: 10.9 years; median: 9.8; IQR: 8.0–13.2).

The overall impact of extending biologic data protection to 10 years would bring the full cohort's total average period of regulatory protection from 10.6 years (median: 9.2; IQR: 8.0–12.7) to 11.1 years (median: 10.5; IQR: 9.8–12.7).

4.3. The impact of CSPs and a 10-year data exclusivity periods

Across all 59 products, the combination of policy changes would impact at least 63% (19 + 18/59) to 69% (23 + 18/59) of the drugs studied, depending upon pending CSP decisions. The combined effect of implementing both policy changes (i.e., CSP and extended biologic data exclusivity) would be to prolong the total period of regulatory protection from an average of 10.0 years (median: 8.5;

Textbox 1
Key terms and facts regarding market protections for new drugs.

Key terms and acronyms	Definition and key facts
CETA	The European Union in the Comprehensive Economic and Trade Agreement (CETA) was the impetus for the institution of patent term extensions (i.e., Certificates of Supplementary Protection) in 2017.
CUSMA	The Canada United States, Mexico Trade Agreement (formally known as the North American Free Trade Agreement) in 2018 is the impetus for initiating the process of instituting an additional 2-years of data protection for biologic drugs.
Drug innovator or originator	A drug originator or innovator is a manufacturer who brought a product containing a new active ingredient never before approved by Health Canada through clinical testing for market entry.
Brand name drug	The innovator's original version(s) of the product containing the new active ingredient.
Biologic drug	Biologic drugs are a category of pharmaceuticals derived from living organisms or from their cells and use relatively new biotechnology. These products are listed under Health Canada's Schedule D.
Biosimilar drug	As biologics are derived using very specific processes exhaustively known only by the originator, equivalents of these drugs made by manufacturers are not considered to be identical and are therefore referred to as "biosimilar" (instead of "generics", which connotes an identical active ingredient).
Small molecule drug	Chemically produced pharmaceutical drugs known as "small molecule drugs" (which represent the majority of drugs available today) can often be synthesized using a variety of processes by different manufacturers to derive an identical chemical structure.
Generic drug	Generics are small molecule drugs with an identical active ingredient as a brand name product, which has been clinically tested and previously deemed safe and effective by Health Canada.
Patent	Patents are issued by the Canadian Intellectual Property Office (CIPO) when a proposed invention is deemed to be (i) novel (i.e., does not already exist in society), (ii) non-obvious (i.e., it makes an inventive step that would not be obvious to other experts in the field), and (iii) useful (e.g., it has commercial applications and can generate new industries). Patents give its holders the prerogative to seek compensation from those who have infringed upon their intellectual property during the patent term (typically 20 years).
Patent linkage	Patent linkage is when patents that are listed in a regulatory bodies' patent register can postpone regulatory approvals for generic and biosimilar manufacturer.
Regulatory market protections	Market protections that implicate Health Canada. These include data exclusivities and patents listed in its register.
Data exclusivity (for innovative drugs or new active substances)	Data exclusivities bar Health Canada from approving applications from generic competitors that seek to demonstrate safety and efficacy by referencing the clinical trial data provided in the drug's originator application for regulatory approval. Innovative drugs (i.e., those containing an active ingredient or new active substance never before approved by Health Canada) are eligible for 8 years of data exclusivity, but this will soon be 10 years for biologics. In contrast, products that are a new version of a previously approved drug receive a 6-year data exclusivity.
Pediatric data exclusivity	Brand name drugs that have been tested in pediatric populations are eligible for an additional six-month exclusivity, which extends the original data exclusivity
Listed patent protection	Patents that have been listed in Health Canada patent register and are subject to patent linkage
CSP	Certificates of supplementary protection extend the protection of one listed patent per product for a maximum period of 2 years.
Unlisted patent protection	Patents that have not been listed in Health Canada patent register and are not subject to patent linkage

IQR: 8.0–11.4) to an average of 11.1 years (median: 10.5; IQR: 9.8–12.7)—an 11% increase.

Assuming generic entry always occurs upon expiration of regulatory protections and a total national expenditure on patented drugs of $16.8 billion, an 11% delay in generic entry amounts to approximately $462 million, $924 million, or $1.4 billion increase in annual costs, depending upon whether generic cost reductions are assumed for one, two, or three or more generic competitors (Table 1). However, taking into account the most conservative assumptions (i.e., only 52% of drugs will receive a generic or biosimilar upon the expiration of the last regulatory protection and that unobserved factors such as additional patents may, on average, prevent generic entry any sooner than 12.3 years), then only 2% of the increase to the average regulatory protection would be due to CSP extensions expiring after the 12.3-year threshold. That said, a 2% delay in generic entry still amounts to $40 million, $80 million, or $120 million increase in annual cost, depending upon whether generic cost reductions are assumed for one, two, or three or more generic competitors. Among the 12 scenarios considered (Table 1), the average increase in expenditure was $410 million.

5. Discussion

Our analysis found that about two-thirds of new drugs will have prolonged periods of regulatory protection as a result of the CETA and CUSMA trade deals. About half of this effect will come from CSPs, and the other half will come from increased data exclusivities for biologics. On average, the collective impact of these policy changes will be to extend the regulatory protection period for new drugs from 10.0 years to 11.1 years. While an 11% delay may appear to be a modest increase, it could equate to as much as $1.4 billion in additional spending per year. However, if one assumes the most conservative assumptions (that only CSPs extended patent protection beyond 12.3 will be most consequential and that only some of these drugs will receive timely generic entry with three generic suppliers), the cost would likely be between $40-$120 million per year (in today's dollars). The average of all scenarios evaluated was $410 million per year, though the wide range of results suggests considerable uncertainty. These findings are a mix of the positive and negative from both a medicine access and a medicine innovation perspective, and demonstrate one approach to assessing the impact of multiple changes to market protections for brand-name drugs.

From a generic medicine access perspective, a positive outcome is that the average expiration of regulatory protections in Canada still appears to be less than 12.3 years. Given that generic entry occurs an average of 12.3 years after Health Canada approval [29], generic entry may commonly occur well after the expiration of regulatory protections and will continue to do so. While this means that the Health Canada register still cannot be relied upon for an accurate sense of when generics will be available (which is a source of considerable uncertainty for payers' spending forecasts), the implication is that the consequences will be limited to specific cases rather than a systemic change. Had our findings been longer than the 12.3-year average, this would signal a more fundamental shift that would delay access to generic medicines more substantially from the current status quo.

A negative outcome of our study from the perspective of generic access is that with the assistance of CSPs, some medicines are likely to see particularly lengthy competition-free periods. Canada's CSP policy does not limit the number of years after Health Canada approval that patent term extension can expire. While this is similar to policies in the European Union [8], even the United States—which is known for the most generous patent protection for pharmaceuticals in the world—has put a limit of 14 years on the amount of time that an extension can delay a patents' expiration beyond regulatory approval [11]. Without such a limit, we found that more than half of CSPs granted expire after the 12.3-year mark and more than a quarter expire after the 14-year mark. Given the CSP eligibility requirements of registering within one year after gaining regulatory approval in peer countries, drugs receiving CSPs are likely to have relatively more patent life remaining prior to receiving an extension as compared to other drugs. The regulatory changes will likely encourage patentees to accelerate submission to Health Canada for some drugs in order to be eligible for CSPs. Ironically, this is the opposite of the typical intent of patent term extension policies, which seek to compensate drug innovators with particularly long development and regulatory review periods by granting them additional post-market patent life.

From an innovation perspective, the move to create longer exclusivity periods for biologics over small molecule drugs is concerning. There is no compelling evidence to suggest that biologic drugs require longer exclusivity periods. Recent studies have found that relative to small molecule drugs, biologic drugs are more often successful during clinical trials (which substantially reduces development costs associated with failed products) [33], and they do not require relatively more time to develop [34,35]. A major reason why biologic drug makers advocated for increased data protection for biologics is due to a fear that patents will offer less secure market protection for this category of drugs. This fear was prompted by the historical experience with small molecule drugs where patents on manufacturing processes offered weak market protection since identical compounds can be derived in a variety of ways [14,36]. However, when it comes to biologic drugs, identical processes must be used (they are "products by process") and are not easily replicated [13]. Enough information to reproduce this process is not disclosed in the patent and these details may more accurately be regarded as a trade secret rather than a patented process [37]. Unlike patents, trade secrets have no expiration. For these reasons, a lack of adequate market protections has not proven to be a challenge for biologics [38,39]; in fact, observers have argued for similar reasons that biologic markets are "natural monopolies" [40,41]. Nonetheless, advocates for brand name biologic drug development are already building upon the momentum gained from the acceptance of extended data exclusivities for biologics through CUSMA and are leveraging this change to argue for similar ones elsewhere, such as Japan [6].

6. Conclusion/policy implications

Our methodological approach may be of immediate service to countries and stakeholders which need to evaluate the impact of multiple proposed changes to brand name drug market protections upon their own country or upon their trading partners, which were either induced by the negotiation of bilateral or multilateral trade agreements or by other domestic pressures. The approach can also be applied within the context of budget planning and the allocation of government funds to those who deliver health services and will bear the downstream cost of these trade concessions in the future, and/or to further justify the role that federal governments should play in efforts to reduce drug costs, such as bulk pricing negotiations [35,42].

Regarding the application of this methodological approach in other countries, modifications will be necessary as Canada and the United States are unique in their linkage of the patent system to the drug regulatory body and the corresponding patent registers [43]. However, issuance of CSPs (also known as "patent term extensions") is practiced by many countries internationally and lists of issued extensions can be procured from the respective patent offices [44]. Extended patents are important since the manufacturer has identified them as key intellectual property, and the expiration of these key patents has been demonstrated to be a reasonably strong predictor of generic entry for top-selling drugs in the United States [16]. Data on other patents can be gathered by using those listed in the Canadian and/or American [45,46] registers and then isolating their local equivalents by using the international patent family groupings available through INPADOC, Derwent, and other databases [47,48].

We further note this methodological approach aims to estimate the proportionate overall increase in expenditures on all drugs containing a new active substance, rather than of individual products; however, the approach described here could be applied to individual products or groups of drugs, assuming expenditures for that product or set of drugs is available. To achieve this, estimates of total spending upon those drugs would be required. It also may be possible to estimate projected future spending on patent drugs should a consistent upward or downward trend be identifiable in the country of interest (assuming no change to the regulatory protections), rather than assuming relatively stable spending, as has been done in the current study.

In closing, when calculating the possible financial changing pharmaceutical patent policies and the corresponding financial implications for the health system, it is important for us to acknowledge the possibility that these intellectual property concessions in trade agreement negotiations may have been offset by broader economic and societal benefits beyond the health sector that are a net positive for the country and may even bring indirect health benefits through improved economic growth (though previous analyses have argued to the contrary [5]). Canada's competition-free period for new drugs has been a key bargaining chip in previous trade negotiations [49]. While the positive benefits of trade may be a silver lining, it has also come at a cost to many sectors, including the healthcare system which already faces crises surrounding increasing drug expenditures with a growing senior population that requires ongoing access to prescription drugs. Furthermore, as there are still key Canadian populations currently without adequate pharmaceutical insurance coverage (e.g., the so-called "working poor"), the consequences of these trade concessions may be felt at the individual level by those who will be exposed to higher drug costs for longer than would have otherwise been the case [50].

Declaration of Competing Interest

The authors declare that they have no competing interests or conflicts of interest.

Acknowledgements

We are grateful to Amir Attaran (University of Ottawa) for preliminary conversations regarding the consequences of extending biologic exclusivities and to Aaron S. Kesselheim (Program On Regulation, Therapeutics, And the Law [PORTAL], Harvard Medical School & Brigham and Women's Hospital, Boston) for input on developing a similar methodological design for evaluating the impact of patent term restoration in the United States.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2019.09.005.

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