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Patent restoration and the cost of pharmaceuticals

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The Parliamentary Budget Officer (PBO) supports Parliament by providing analysis, including analysis of macro-economic and fiscal policy, for the purposes of raising the quality of parliamentary debate and promoting greater budget transparency and accountability.

This report estimates additional drug costs to Canadian consumers from changes to the Patent Law as negotiated under the Canada-European Union Comprehensive Economic and Trade Agreement (CETA). A two-year certificate of supplementary protection (CSP; elsewhere termed *patent restoration,* and used synonymously here since CSP provides patent-like protection) will delay the introduction of generic alternatives, and likely keep prices higher than they otherwise would be. The report also estimates the fiscal cost to the federal government of compensating provinces for increased costs to provincial public drug programs.

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Glossary

ATC	Anatomic Therapeutic Chemical (ATC) Classification System
CETA	Canada-European Union Comprehensive Economic and Trade Agreement
CIHI	Canadian Institute for Health Information
CIPO	Canadian Intellectual Property Office
CSP	Certificate of Supplementary Protection
DIN	Drug Identification Number
IQVIA Canada	IMS Health and Quintiles
NHEX	National Health Expenditure Database
NOC	Notice of Compliance
NPDUIS	National Prescription Drug Utilization Information System
PMPRB	Patented Medicine Prices Review Board
PTR	Patent Term Restoration
WHO	World Health Organization

Executive Summary

Bill C-30, *An Act to implement the Comprehensive Economic and Trade Agreement (CETA) between Canada and the European Union (EU)*[1], received Royal Assent in May 2017. It took effect on September 21, 2017.

Part of the legislation included two provisions in particular that would affect Canada's patent laws concerning pharmaceutical products. These provisions concern a prolonging of the 20-year period of patent protection afforded drugs containing a new medicinal ingredient, or a new combination of medicinal ingredients.

Bill C-30 introduces so-called certificates of supplementary protection (CSP), which provide up to two years of additional protection after the expiry of a patent. The purpose of this "patent term restoration" is to compensate patent holders for delays in obtaining regulatory approval for their pharmaceutical products because of the need to prove their safety and effectiveness.

However, a consequence of the change is to delay introduction of cheaper generic versions of popular drugs,[2] thus preventing consumers and private/public drug plans from taking advantage of lower-cost sources.

As implemented, the provision is limited to new medicinal ingredients or combinations, estimated at about one-third of patented drugs in 2015 (34 per cent, by sales value). This took effect on September 21, 2017.

Similar provisions already existed in other countries where patent restoration can last up to five years.

This report focuses on spending by Canadians, both nationally and for public drug programs. Since the federal government made a commitment to compensate provinces for increased expenditures in the public plans, this report extends that analysis to examine the fiscal cost to the federal government.[3]

In 2015, Canadians spent $15.2 billion on patented medicines (PMPRB, 2016). Including fees and markups adds roughly 25 per cent more to their spending. For a family of three, this works out to more than $1,272. Innovative drugs represented about $4 billion of those sales.[4,5]

In this report, PBO estimates the annual cost of the two-year CSP. Since none of the drugs already marketed in September 2017 is eligible for a CSP, this report provides an illustrative analysis to gauge its impact. That is, it estimates the increase in expenditures if the two-year CSP had been available to innovative drugs sold in 2015.

Since the value of year-to-year patent expirations fluctuates significantly, some averaging is needed to avoid having peaks and troughs distort the estimated impact of CSP. This is done by using the average annual value of patent expirations between 2015 and 2024 (multiplied by two). That value is used to determine the basis for prolonged expenditures on patented innovative drugs.

PBO's analysis shows that the increase in expenditures nationally would have reached roughly $392 million (annually, 2015 dollars) had CSPs been fully in place in 2015. For provincial public programs, the cost would have been $214 million.

Summary Table 1 CSP-induced regional annual expenditures (2015-based)

($ millions)	**Cost to Public Programs**	**National Cost**
Alberta	14.6	38.8
British Columbia	28.2	42.2
Manitoba	5.8	9.4
New Brunswick	2.1	8.9
Newfoundland	1.4	4.5
Nova Scotia	1.5	9.6
Ontario	105.5	180.8
Prince Edward Island	0.2	0.8
Quebec*	49.3	89.6
Saskatchewan	5.1	7.4
Total	**214**	**392**

Note: Costs exclude institutions such as hospitals and care facilities. They are based on the average value of patent expirations for innovative drugs between 2015 and 2024. The first column excludes that incurred by private plans and non-insured individuals within each province.

* Data source is different from other provinces; IQVIA Canada, rather than NPDUIS as with other provinces.

Source: Cost to Public Programs (except Quebec): PBO calculations using data from NPDUIS (Canadian Institute for Health Information). National and Quebec's public program costs: PBO calculations using GPM data from IQVIA Canada.

Given the rapid evolution of the Canadian drug market, this estimate is likely to understate future expenditures. (See Appendix B, particularly the discussion of biological drugs).

These estimates do not include drugs dispensed in institutions such as hospitals, clinics and care facilities. When those are included, the national cost estimate would reach more than half a billion dollars (assuming the ratio of innovative to non-innovative patented drugs in those areas is similar to that reported above: 34 per cent).

These estimates differ from earlier work primarily because the pool of drugs to which CSP applies is smaller in this study (the implementing regulations of CSPs limited it to innovative drugs, whereas previous studies assumed it would apply to all patented drugs). This is in spite of the use in this report of a larger discount after the drugs lose patent protection.

PBO's estimated costs are based on the difference between the average costs of innovative patented drugs versus a broader group of non-patented prescription drugs. Since not all patented drugs are followed by generic versions, and the price of a brand-name drug is not fixed after its patent expires[6], this is a potentially important distinction.

By making the comparison one of innovative versus non-patented prescription drugs, which is PBO's methodology, the analysis also comes closer to determining the long-term cost of CSPs. This is because it accounts for the full transition of the cost of the drug from an innovative one under patent to a more common non-patented prescription drug.

1. Background

Bill C-30 to implement the Comprehensive Economic and Trade Agreement (CETA) between Canada and the European Union (EU) received Royal Assent in May 2017. It took effect on September 21, 2017. Part of Bill C-30 included two provisions in particular that would affect Canada's patent laws concerning pharmaceutical products.

The changes in question concern a prolonging of market exclusivity for drugs containing a new medicinal ingredient, or a new combination of medicinal ingredients. This would delay the introduction of generic drugs, thus preventing consumers and private/public drug plans from benefitting from lower-cost sources.

This report focuses on the implications of the period of market exclusivity: its cost for Canadian consumers, both nationally and provincially. It also extends this analysis to examine the fiscal cost to the federal government since there was a commitment made to compensate provinces for increased expenditures.

The following sections explore existing forms of protection for drugs and the implications of CETA. Section 4 details calculations and a cost estimate.

2. Forms of Protection for Drugs

Prior to the implementation of CETA, there were two primary forms of protection for drugs: patents, and data protection for *innovative* drugs. An innovative drug is defined by Health Canada 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".[7]

Patent protection begins when a patent application is filed. Data protection begins at the time a new drug is approved, once a notice of compliance (NOC) has been granted.

Health Canada approves a drug for sale and grants an NOC when criteria for safety and effectiveness of the drug have been met.

Box 2-1: Definition of 'drug'

In Health Canada's Patent Register, as well as Health Canada's Drug Database, drugs are identified by a drug identification number (DIN).

A drug can be sold in various doses (or strengths) and forms (for example, a spray or a pill). To uniquely identify the combinations of medicinal ingredient, strength, form and route of administration, each instance of the drug is assigned a DIN. Therefore, the same medicinal ingredient may be available in many drugs.

A medicinal ingredient can also be combined with others medicinal ingredients in a drug. This combination is itself reflected by a unique DIN. These combinations can also vary in their strength, route of administration and form.

2.1. Notice of Compliance

In Canada, as in other countries, pharmaceutical companies are required to prove a drug's safety and effectiveness before it can be marketed. This process involves tests and trials that can take years to complete. Since drugs often fail in clinical trials, the delay is a necessary part of the process to ensure that laboratory results hold up in more widespread use.

When those trials are successfully completed (that is, when the manufacturer has demonstrated that the drug is safe and effective), Health Canada issues an NOC allowing the product to be marketed. Under some circumstances, an NOC can be following a shorter review time-frame, although there may be conditions attached that require the manufacturer to undertake additional work.[8]

2.2. Patents

When a drug receives a patent, Canadian law provides pharmaceutical manufacturers with 20 years of market exclusivity from the date of filing the patent application. A single patent may protect several drugs in a particular combination, and a single drug may have multiple related patents. These patents may be granted for a variety of inventions, including the active ingredient, coatings, therapeutic indications, dosing, manufacturing methods and other aspects of the drug.

The Canadian Intellectual Property Office (CIPO) publishes all patents. Health Canada maintains a Patent Register of patents that meet a set of specific regulatory requirements for pharmaceutical products. However, including patents on the Patent Register is not mandatory for drug manufacturers, and not all patents may be eligible for inclusion (see Appendix B). Therefore, the process of determining whether a drug has had its patent(s) expire can be cumbersome as well as expensive.

Any manufacturer wishing to sell a generic version of a drug must address all the patents on Health Canada's Patent Register before obtaining market authorization from Health Canada (a Notice of Allegation).[9]

For Canada, the lack of good documentation concerning all patents related to a particular drug (and their expiration) contributes to substantial litigation between patent holders and generic manufacturers (see Appendix C, section 2). Indeed, patent holders may have unlisted patents that they only assert after a generic or biosimilar drug has launched (White and Liptkus, 2017).

For our analysis of patents applying to brand drugs, PBO therefore supplemented the Patent Register list with drugs using DINs appearing in the Patented Medicine Prices Review Board (PMPRB) annual report (PMPRB, 2016). Following a decision at the World Trade Organisation (WTO, 2000), it

has been illegal to manufacture a drug (for stockpiling) before its patent has expired.

2.3. Data Protection for Innovative Drugs

A drug manufacturer may obtain a period of data protection for a drug that is innovative. These are defined as drugs that contain a medicinal ingredient not previously approved in a drug and that is not a variation of a previously approved medicinal ingredient, such as a salt, ester, enantiomer, solvate or polymorph.[10] Between 2007 and 2015, an average of 26 innovative drugs for human use were introduced each year (Health Canada Register of Innovative Drugs), whereas on average about 98 patents were listed annually in the Health Canada's Patent Register.

If granted, data protection for an innovative drug provides the manufacturer with eight years (eight years and six months if pediatric data is provided) of market exclusivity. Data protection begins when an NOC is issued for the innovative drug.

Thus, any manufacturer wishing to sell a generic of an innovative drug cannot file a submission with Health Canada for the first six years of the eight-year period of data protection. Furthermore, an NOC will not be issued to a generic manufacturer until after the end of the eight-year (or eight years and six month) period.[11]

3. Implications of CETA

The implementing legislation, Bill C-30, provides an additional period of protection for drugs containing a new medicinal ingredient or a new combination of medicinal ingredients, protected by an eligible patent.

Health Canada implements this provision of the trade agreement by awarding a certificate of supplementary protection (CSP), which provides patent-like rights following the patent expiry. The maximum term for a CSP is two years.

The patent holder has latitude in choosing which patent to apply for a CSP. In 2015, innovative drugs represented some 34 per cent of all patented drugs by sales. CETA also contains a provision for data protection, but this simply locked in the practice already in place.[12]

In sum, an additional period of protection of up to two years after the patent expiry may be available following the implementation of CETA. However, the period of data protection remains unchanged at eight years.

3.1. Patent Term Restoration

The gap between the time a patent application is filed and the date that market approval is granted can be substantial. Grabowski and Vernon (2000) showed that in the United States, this reduced an effective patent life to less than 12 years.

In Canada, prior to the legislation that implemented CETA, a facility to recover some of that delay did not exist.[13] This has now been changed for innovative pharmaceutical products. It is not limited to those originating in the European Union, even though the impetus for the change was the CETA trade agreement.

In many countries (for example, Europe, Japan and the United States), patent restoration has existed for some time now. In those cases, it can be up to five years, and is also limited to drugs that are innovative. Some even impose supplementary conditions. As an example, in the United States, patent restoration is not allowed to extend market exclusivity beyond 14 years.

3.2. Certificates of Supplementary Protection

To implement Canada's requirements under CETA, the Patent Act has been amended to create a CSP. The term of a CSP is calculated by subtracting five years from the period beginning on the patent's filing date and ending on the day an NOC is issued, up to a maximum of two years.

For most patents, the term of a CSP will be two years, given that it usually takes more than seven years from filing a patent application to obtain an NOC for a new medicinal ingredient.[14] In cases where approval takes between five and seven years, the term of a CSP will be between 0 and two years. The Minister of Health is granted discretion to reduce the term of a CSP when the Minister finds that there was unjustified delay on the part of the pharmaceutical company.

Thus, a patent life for an innovative product begins when the patent application is filed. It reaches a milestone when an NOC is issued, then provides the patentee with exclusive rights until the patent expires. A CSP will extend that latter period by up to two years. To obtain a CSP, the patent holder must show that: [15]

- the patent pertains to a medicinal ingredient for which an NOC was issued;
- the NOC is the first that was issued with respect to that medicinal ingredient;
- no other CSPs have been issued with respect to the medicinal ingredient or the combination of medicinal ingredients.

The second requirement is important since a large portion of the drugs listed in the Patent Register are not eligible to be listed in the Register of Innovative Drugs (some 66 per cent by sales value). Health Canada maintains the Register of Innovative Drugs for enforcing data protection for new medicinal ingredients.

Though the criteria for inclusion in that register are similar to the basis for granting CSPs, there are some differences. For example, a combination of two previously approved medicinal ingredients can be eligible for the CSP; however, this combination is not eligible for data protection as an innovative drug since the medicinal ingredients within the combination have already been approved. This would mean that the pool of CSP-eligible drugs is somewhat larger. But more variations of medicinal ingredients are excluded from CSP so the difference is not necessarily large.

The analysis in this report uses the Register of Innovative Drugs to calculate the cost of the CSP regime had it been in force in 2015. As there are more CSP-eligible drugs than listed in the Register of Innovative Drugs, the cost may be somewhat understated (Appendix C).

The second requirement listed above is also further limiting for pharmaceutical companies since it restricts which patent can obtain the extension: medicinal ingredient versus use of the drug. Pharmaceutical manufacturers obtain patents in a first filing, but sometime later obtain additional patents for different applications of the same medicinal ingredient. Only first medicinal ingredients, or a particular use, are eligible for CSP.

For example, Sildenafil Citrate was first patented as the medicinal ingredient in a treatment for pulmonary arterial hypertension. Years later, it was patented as a treatment for erectile dysfunction. Sales of the second use dwarfed the sales of its first use. While either use is eligible for a CSP, the medicinal ingredient is not eligible in the second use.

Also important is that the CSP will only apply to drugs that receive a NOC on or after September 21, 2017. This means that its effect will only gradually be felt, and will not start for years.

One notable exception is that a CSP will not provide protection to innovators seeking to prevent generic pharmaceutical companies from exporting patented drugs.

This is something of a reversal of the patent law change in 2000 that prohibited the manufacture and stockpiling of patented drugs before the patent expired. That is, though the sale of drugs still protected by a CSP will not be permitted, manufacturing drugs to supply export markets will be permitted.

3.3. Implications for Consumers

The effect of the CSP, which is intentional, will be to delay the availability of generic equivalents of patented pharmaceutical products. This is important because popular patented drugs tend to maintain their prices even after the patent has expired (see discussion of Table B-1 in Appendix B).

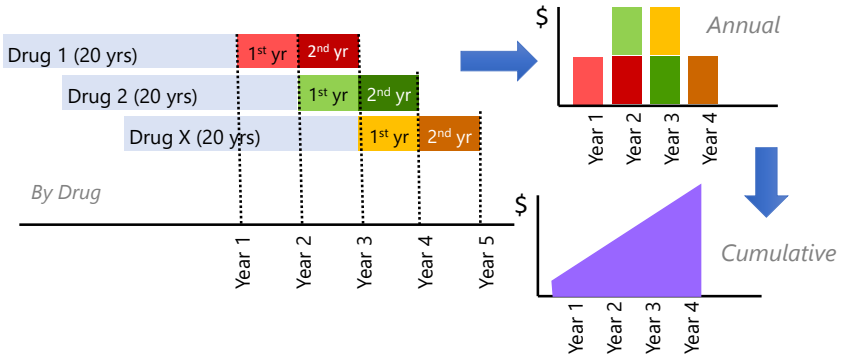
In other words, only the availability and adoption of generics lower drug costs. The CSP regime, implemented to meet the requirements of CETA, will keep drug prices higher than they would have been, for up to two additional years.

To illustrate, consider a drug (Drug 1) that is coming to the end of its 20-year patent. Under a baseline scenario where CSPs did not exist, a generic drug could come to market in Year 1. The use of the generic drug would create a savings equal to the difference between the price of the generic and the price of the patented version.

Instead, the CSP extends the sale of Drug 1 at its patented price for up to two years, precluding the savings. The lost annual saving accumulates over time (see simplified illustration in Figure 3-1).

While not all patented drugs are followed by generic versions, or followed in the span of two years after patent expiration, it is commonplace.

Figure 3-1 Visual presentation of the costs of CSP



Note: Each coloured box represents the value of the difference in the price of the patented drug and the generic, and corresponds to the year in which it would take place.

Because those generic products cost substantially less than the patented product, the delay will increase costs for consumers and insurers.[16] Indeed, many provinces and private drug insurance plans limit reimbursement of interchangeable generic drugs to the price of the generic, as a cost-savings measure.

So, the reduced cost for a drug is immediately evident when a patent expires and either a generic is made available, or the cost of the brand-name product falls.

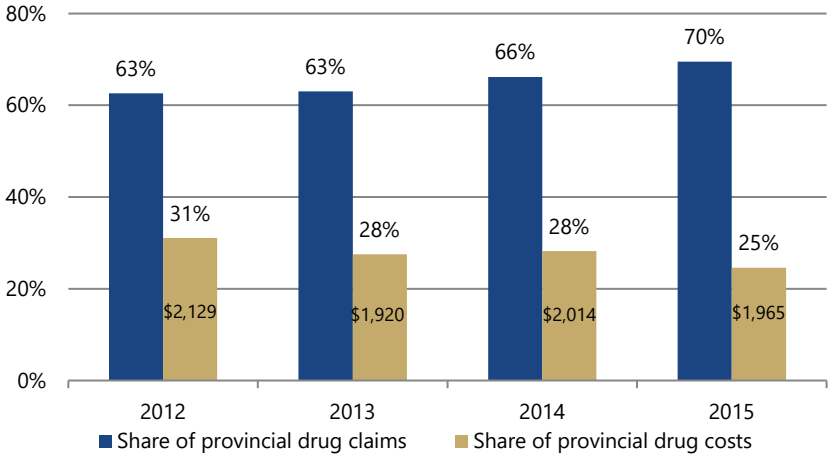
3.4. Implications for Provinces

Over time, the use of generics has played an increasingly important role in holding down expenditures on public health plans (Figure 3-2; see Appendix B for more discussion concerning the dynamics of Canada's drug market).

The CSP regime thus has the potential to set back those cost-containment efforts that provinces were working to achieve.

Figure 3-2 Generic pharmaceuticals in use and cost (public drug plans)

Units, $ millions, and percentage



Sources: NPDIUS database, May 2017.

Note: This accounts only for drug costs. It omits dispensing fees and markups.

3.5. Implications for the Federal Government

As part of its negotiations for CETA, the federal government stated that it would compensate provincial public plans for adverse fiscal impacts arising from the extra period of market exclusivity.[17] This report provides a cost estimate for that commitment.

There are also direct drug costs in some areas of health care under federal purview.[18]

4. Analytical Backdrop

Existing studies of the cost of "patent extension" illustrate that costs are sensitive to underlying methodology. In particular, the price reduction that occurs when a patent expires heavily influences the estimated cost. Rebates from manufacturers, as well as the existence and number of generics in particular, influence the price to consumers.

This makes it difficult to project the cost, even with detailed knowledge of how the CSP is implemented. Indeed, many provinces are now using tiered pricing that is dependent on the number of generics available. This means that predicting the price gap between a generic and brand-name drug requires a simultaneous prediction of the number of generics that will enter.

Moreover, brand-name manufacturers themselves often introduce generic versions, referred to as "authorised generics". So, with tiered pricing, they can influence the price that independent generics will get for their products.

The Competition Bureau (2007; Chart 1) illustrated that the number of generics entering the market is correlated to the sales of the brand-name product. So less popular drugs may have few, or no generics. Indeed, it was the lack of competition for small-population off-patent specialty drugs that led to large increases in some prices during 2015.[19]

The remainder of this section will describe in more detail issues that must be addressed in estimating the cost of CSP. To begin, two core pieces of information are needed: the dollar sales of innovative drugs losing patent protection; and, the cost difference between innovative and non-patented prescription drugs (for human use).

4.1. The Dataset

PBO first merged the Register of Innovative Drugs with Health Canada's Patent Register, then combined that with the GPM data from IQVIA Canada and the NPDUIS database to account for sales of innovative and patented drugs (2015 for IQVIA Canada, 2011 to 2016 for NPDUIS; Appendix C).

This final database contained a list of drugs (based on DIN) including the sales and volume, that were sold in pharmacies in Canada, and those restricted to public drug plans. These sales exclude markups and fees, and only reflect the price of the product. Markups and fees tend to be constant – so they are a larger proportion of the cost of generics – but there is, nonetheless, some variability, which would lead to an understatement of the cost of CSPs.

The Register of Innovative Drugs provides a list of drugs that are innovative. The Patent Register provides a list of drugs and their patent information (such as patent number and expiration date). One drawback of using the Patent Register is that not all patented drugs are reported there.

The Patent Register is voluntary (see Appendix C), whereas CIPO contains the full list of patents. The Patent Register, however, is where information specific to pharmaceutical products (DINs, etc.) is reported.

PBO estimates that as much as 15 per cent (by sales value) of patented drugs may be missing from the Patent Register. So, matching the Register of Innovative Drugs with the Patent Register will under-report the drugs that have patented innovative ingredients. To remedy this, PBO supplemented this list with patented drugs reported to the Patented Medicine Prices Review Board (PMPRB, 2015).

GPM data from IQVIA Canada provided total consumption and expenditures by province and majority payer (that is, public programs, consumers or private plans), excluding any markups and fees. Sales and volume were estimated based on a large sample from retail pharmacies across the country. It excludes direct sales to hospitals and other facilities.

Unlike the GPM data from IQVIA Canada, data on sales and volume from NPDUIS data provided by CIHI are administrative, meaning NPDUIS data better reflect the expenditures public plans incurred or reimbursed. However, NPDUIS does not contain data for Quebec's public plan.

Therefore, PBO estimated the implications of CETA on Quebec's public plan using the GPM data from IQVIA Canada where the majority payer was identified as public.

Key information allowed PBO to identify which sales and volume were:

- patented and innovative;
- patented, but not innovative;
- not patented and not innovative.

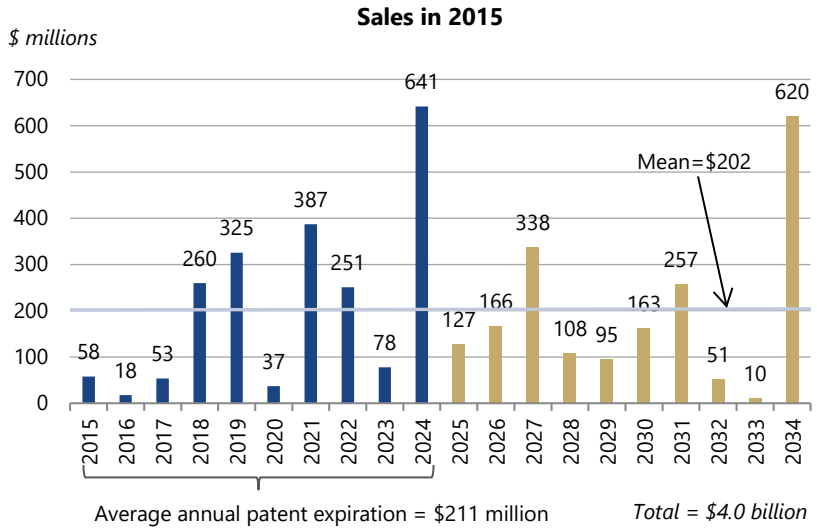
Additional information also permitted PBO to group drugs based on whether they were brand-name, generic, biologic or over-the-counter. This made it possible to estimate the annual value of patents that expired, including future patent expirations.

4.2. Value of Lost Patent Protection

Using the data described above, PBO determined that between 2015 and 2024, an annual average of $211 million of sales of drugs that were designated as innovative drugs would lose patent protection (Figure 4-1). This assumes that in each case it is the last patent that is extended (prior to a CSP).

This is similar to the $202 million that would be the annual average from 2015 to 2034 (Figure 4-1). However, it is likely that additional products, patents for which will expire before 2034, will receive market approval in the coming years. This would increase the longer-term average.

Figure 4-1 Expenditure on innovative drugs in 2015 by year of patent expiration



Sources: Health Canada Patent Register (2017), Innovative Drug database (2017), IQVIA Canada, GPM data (2017), NPDUIS (2017).

Note: The period 2015 to 2024 is used to determine the average annual patent expiration that underlies the calculation of additional expenditures. See Box 4-1 and Appendix C for more details regarding the underlying data. Sales add up to the total of expenditures on innovative drugs in 2015. Note that there is some possibility, albeit small, that more innovative drugs may receive an NOC for a patent that expires before 2024.

The peak in patent expiration in 2034 is for hepatitis drugs (Harvoni). Those drugs will not be eligible for a CSP, given that they were already on the market in September 2017.

If they had been eligible, their exceptional expenditure means that for two years, the additional cost would have been quite large; since they are not

biological dugs (see Appendix B, Section 3), the drop in cost after patent expiration is expected to be very large.

The data illustrated in Figure 4-1 have been compiled from databases that use DINs as the identifier for each entry (see Box 2-1). The relationship among DIN, patented drugs and medicinal ingredients is interwoven and needed to be separated to estimate annual values of expiring patents for innovative drugs (Box 4-1 and Appendix C).

Doing so resulted in a list of DINs for drugs that contain at least one innovative medicinal ingredient that had patent protection in 2015, and would have been a candidate for a CSP.

Box 4-1: DINs, innovative drugs and patents

A Drug Identification Number (DIN) is a computer-generated eight-digit number assigned by Health Canada to a drug product prior to being marketed in Canada. It uniquely identifies all drug products sold in a dosage form in Canada and is located on the label of prescription and over-the-counter drug products that have been evaluated and authorized for sale in Canada.

Since a patented drug may be relevant to different drugs (for example, different dosage forms or strengths), a patent might appear on the Patent Register in relation to several DINs.

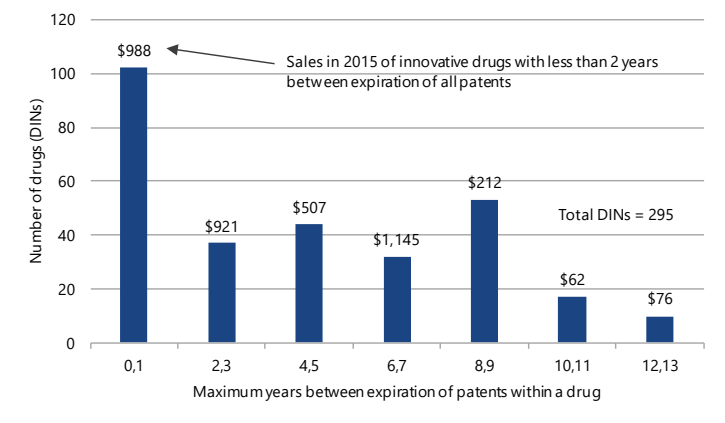
A medicinal ingredient may also have several patents that apply to the treatment of different maladies, not to mention off-label prescribing.

Certificates of supplementary protection will be issued in respect of to the first market approval (NOC) for a new medicinal ingredient, a new use of a medicinal ingredient, or combination of medicinal ingredients. There may be multiple patents relevant to the medicinal ingredient or combination of medicinal ingredients. Pharmaceutical manufacturers may have considerable latitude to choose the patent in respect of which to apply for a CSP.

While in most cases this would be the last expiring patent, this need not always be the case. A CSP is applicable to drugs containing the medicinal ingredient, or use, as set out in the CSP. So, for example, an earlier expiring patent related to a CSP-candidate NOC that is more widely relevant to other drugs containing the same medicinal ingredient may be more valuable. In that case, companies may be more likely to apply for a CSP for a more valuable patent, even though it expires sooner.

Box 4-1: continued

To gauge the latitude that firms have, consider that about three-quarters (by value) of the innovative drugs sold in 2015 had a gap of at least two years between the first and last patents to expire (Box Figure).



Note: For drugs sold during 2015. The horizontal axis shows the years between patent expirations. So, the second column (2, 3) reports patents that have either two or three years between the expiration of the first and last patents. The column labels report the value of sales in 2015 of drugs with patent expirations as indicated on the horizontal axis. For example, there was $988 million in sales for drugs that had fewer than two years between expirations of all patents. Some patents that are common to other drugs have been removed in an attempt to identify patents unique to innovative drugs.

4.3. Cost Difference between Innovative and Non-patented Drugs

CSPs effectively result in up to two additional years of higher drug prices than may have otherwise existed.

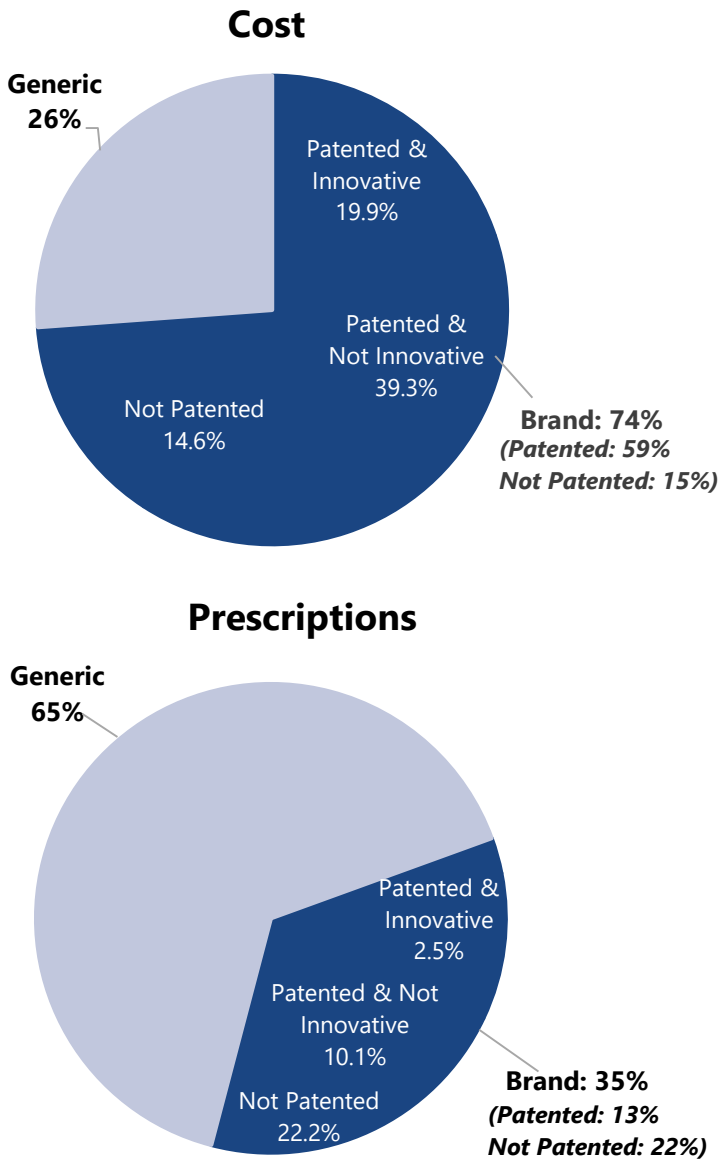
Key to calculating the cost (annual) of CSPs is the difference between the price of a patented drug, and the price that would prevail after the patent expires.

In this report, PBO uses the price gap per prescription observed in the IQVIA Canada's GPM database and the NPDUIS database in 2015 between innovative patented drugs and non-patented prescription drugs. In that case, the average prescription for an innovative patented drug was 17 times more expensive than the average prescription for a non-patented drug (combined brand-name and generic). See Figure 4-2 and Box 4-2.

Implicit in using the factor of 17 is that, first, all innovative drugs will eventually become commonplace prescription drugs and, secondly, a CSP

delays this happening by two years. In effect, the assumption is that the average price of today's innovative drugs will eventually match the average price of today's non-patented prescription drugs.

Figure 4-2 Pharmaceuticals in prescriptions and expenditures in 2015/16



Sources: IQVIA Canada, GPM database, 2017

Note: Prescriptions for over-the-counter drugs are omitted. Drugs used in hospitals are not included, and are predominantly patented drugs. In reporting the cost, dispensing fees and markups have not been included. These are generally a fixed cost of every prescription, and therefore distort the relative cost of generic medicines.

The comparison sometimes made between generic drugs and their brand-name counterparts can be misleading since not all brand-name drugs are patented, and some brand-name manufacturers produce their own generic versions.[20]

Box 4-2: Relative cost of drugs

By identifying the explicit group of drugs that would have been eligible for patent restoration had it been in place in 2015, PBO was able to calculate the price of eligible drugs (by prescription) relative to the price of all non-patented products (first row in Box Table).

This comparison represents the price gap that PBO uses for estimating the cost of two additional years of patent restoration.

Figure 4-2 also makes other comparisons of relative cost possible. Thus, innovative patented drugs are about 20 times more expensive than generic drugs (as a group). Patented drugs are about 10 times as expensive as non-patented drugs.

The following table also demonstrates the importance of measuring this price gap between the appropriate groups of drugs.

Box Table

	Numerator Sales:Volume	**Denominator Sales:Volume**	**Relative Cost**
Patented & Innovative vs. Non-patented	**(19.9/2.5) =8**	**(40.8/87.4) =0.5**	**(8/0.5) =17.2**
Patented & Innovative vs. Generics	(19.9/2.5) =8	(26.2/65.4) =0.4	(8/0.4) =20.1
Patented vs. Non-patented	(59.2/12.6) =4.7	(40.8/87.4) =0.5	(4.7/0.5) =10.1
Brand-name vs. Generics	(73.8/34.6) =2.1	(26.2/65.4) =0.4	(2.1/0.4) =5.3

Source: PBO calculations using data from IQVIA Canada's GPM data

Since there are many drugs in each group, differences such as form and dosage should be statistically neutralised on average. A small bias in the size of prescriptions for patented drugs versus generic drugs is also not large enough to substantially alter the calculated ratios.

Note: Data from NPDUIS (2018) produces similar results where comparable.[21]

This comparison across broad groups is more long-term in nature since the average price within each group represents a defining characteristic of each.

That is, if a sample of drugs were to exit one group and move to another, its average price should change from that of the first group to that of the second. So, the average price of a representative sample of drugs that moved

from innovative to non-patented should evolve from an average price of innovative drugs to that of non-patented drugs.

This snapshot of the relative price of prescription drugs is for a single year, but the size of the sample makes it unlikely to change much from year to year. Over the longer term, there have been significant changes in the drug market that could substantially alter the cost ratio of 17. For example, omitting biological drugs (which have been gaining market share) lowers the cost ratio to 15.

5. Cost of CSPs

PBO estimated the annual cost of CSPs (patent term restoration) for public drug plans (less Quebec) using data from NPDUIS, and estimated a national cost (with and without Quebec) using data from IQVIA Canada. PBO also estimated the cost to Quebec's public program using data from IQVIA Canada.

This cost is based on prescription drug sales for the 12-month period preceding July 2016, though it takes account of sales of products, the patents for which were due to expire between 2015 and 2024.

Issues that impact on a future projection of that cost concern: the changing share of generics in sales and prescriptions; the role of biological drugs; and price dynamics after patent expiration. These are not treated here, but are discussed in more detail in Appendix B.

5.1. National cost

Recall that the average annual value of expiring patents for the period 2015 to 2024 was an estimated $211 million (see Section 4.2). And, since patented innovative drugs were, on average, 17 times more expensive than non-patented drugs, the discount factor is equal to 94 per cent (see Section 4.3).[22]

Combining the average annual value of expiring patents for the period 2015 to 2024 with that discount factor, the estimated annual foregone savings from a two-year CSP is $392 million (using the calculation illustrated in Figure 3-1).[23]

This estimate is arguably an annual cost over the long term because it accounts for the complete horizon of moving patented innovative drugs to the status of common prescription non-patented drugs. In principle, it also incorporates the decline in the price of brand-name and generic drugs over time.

More precisely, when a drug loses patent, it starts on a path that makes it a commodity, selling at a price closer to its cost of production. The analysis here calculates cost as if CSP delays the date at which the drug reaches commodity status by two years. So, it accounts for the extra expenditures over the full horizon caused by the delay.

An alternative short-term estimate of the cost of CSP is consistent with this long-term result by calculating a smaller two-year effect of generic drugs (Appendix A).

The $392 million annual figure is lower than the estimate of $795 million produced by Lexchin and Gagnon (2014), even though theirs was only for the short-term foregone savings.

The difference is even more pronounced when considering that Lexchin and Gagnon's estimate was for the year 2010. At that time, expenditures on pharmaceuticals were 18 per cent lower than in 2015, and inflation alone would have increased the value of 2010 sales by almost 10 per cent.

However, the difference in the estimates narrows somewhat when considering that 20 per cent of their cost is caused by changes in the Right of Appeal by patentees when a generic manufacturer attempts to enter the market.[24]

Nonetheless, the main factor explaining the difference in estimates is the group of drugs to which the CSP applies – even after accounting for the different base years for the analysis.

In their work, the extension applied to 10 per cent of all patented drugs (by expenditure) for one year. In this report, it applies to 2 per cent of patented drugs for two years. This is equivalent to 4 per cent of patented drug sales in one year. PBO (2017) similarly used the wider array of drugs (10 per cent of all patented drugs) in its analysis and overestimated the transfers that would leave Canada.

5.2. Cost to Public Drug Plans and the Federal Government

Of particular interest is an estimate of the fiscal impact on public plans. This is especially germane given the federal government's statement at the time of negotiating CETA that provinces would be reimbursed for additional costs caused by the CSP.

As with the national estimate, the amount of sales moving off patent is calculated using the annual average value of expiring patents for innovative drugs for the period 2015 to 2024. However, the sales here are those paid for public plans. This is discounted by the provincial price ratio between innovative drugs and non-patented drugs. Other factors, such as the schedule of the value of patent expiration, are assumed to mirror the national average.

The ongoing fiscal cost to provincial public plans for CSPs would have been $214 million had that facility been fully in place in 2015 (versus $392 million when private sector costs are included; Table 5-1, see note regarding exclusions).

Table 5-1 Estimated public-plan impact of CSP based on expenditures in 2015

	Alberta	British Columbia	Manitoba	New Brunswick	Newfoundland	Nova Scotia	Ontario	Prince Edward Island	Quebec*	Saskatchewan	Total
Cost shares											
Innovative	20%	21%	13%	14%	14%	11%	28%	7%	19%	14%	**23%**
Non-patented	37%	42%	47%	46%	57%	53%	35%	50%	41%	42%	**39%**
Prescription shares											
Innovative	2%	1%	1%	1%	0%	1%	3%	0%	2%	2%	**3%**
Non-patented	88%	90%	92%	91%	95%	91%	87%	90%	92%	87%	**88%**
Innovative drug cost ($m)	146	278	58	21	14	15	1,058	2	493	52	**2,137**
Estimated cost increase ($m)	**15**	**28**	**6**	**2**	**1**	**2**	**105**	**0**	**49**	**5**	**214**

Note: Costs exclude institutions such as hospitals, clinics, and care facilities. It is based on the average value of patent expirations between 2015 and 2024.

Source: PBO calculations using NPDUIS (CIHI 2017);

*PBO calculations using GPM data from IQVIA Canada.

Expenditures on innovative drugs in Quebec are not included in NPDUIS, but have been factored into the total cost ($214 million) using IQVIA Canada's GPM data. Those in hospitals and institutions, which are covered by provinces, as well as the more expansive coverage of CSPs, would add more to the estimate of provincial costs.

If the proportion of innovative drugs used in those institutions were similar to that of the retail market, then it would amount to an additional 25 per cent. In 2015, when these other factors are included, this would have had a noticeable impact on the fiscal position of the federal government.

The additional cost represents a roughly 1.5 per cent increase in drug expenditures in the provinces on average, or less than a half per cent increase in their health expenditures.

If the federal government maintains its commitment to reimburse provinces for the additional cost to their public drug plans, the estimated cost to the federal government is equivalent to the estimated cost for public drug plans, plus an additional 25 per cent for hospitals and other institutions – roughly $270 million per year.

Since provinces have already expanded substitution of brand-name by generic drugs, and generic drug pricing has been aggressively lowered, there is limited scope for additional savings from generics. So the increased costs will be difficult to deflect.[25]

Appendix A: Alternative Short-term Cost of Patent Term Restoration

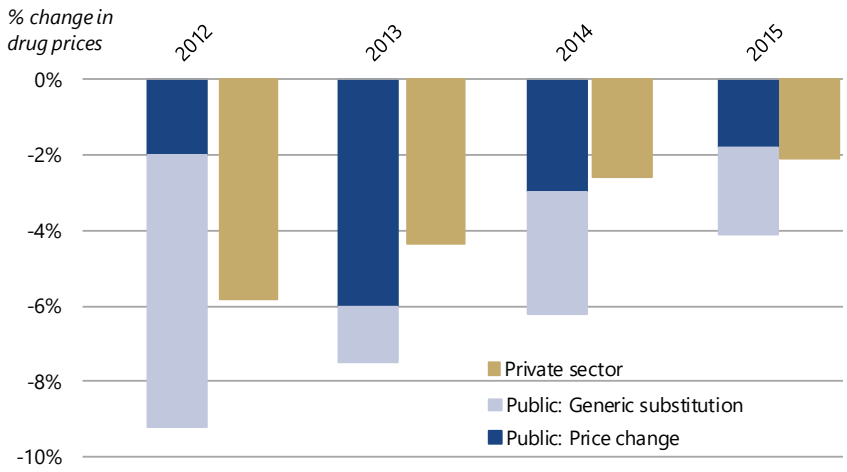
Published price indexes also provide a means to calculate the cost of CSP (short-term). In this case, the sub-component of those indexes that outlines the impact of generics on overall prices can be used to estimate the annual savings. Foregoing those savings for two years would be the cost of CSP.

For 2015, there are two relevant sources of data on price changes attributable to generics: one for public drug plans, and one for private drug plans. In the public plans, the price change was 4.1 per cent (Figure A-1). In private plans, it was 2.2 per cent (Figure A-1). When combined, the overall rate of prescription price change that was caused by generics was 3.0 per cent.

This price change can be decomposed into two parts: generic substitution and sticker-price changes. The generic substitution part is the direct result of moving from patented to generic drugs. The sticker-price change is the measurable reduction in listed prices for drugs, that is, the change in the average price of drugs that can be attributed to the lower price of generics.

For 2015, the aggregate generic substitution component is 1.7 per cent, and the sticker-price effect is 1.3 per cent.

Figure A-1 Sources of price change attributable to generics



Sources: CompassRx, May, 2017; PMPRB, 2016.

Note: The public-sector data have been broken into their two components. Both can be attributed to the presence of generic drugs since it is the competition from generics that leads to reductions in the price of brand-name drugs. Indeed, the large price change in 2013 could be attributable to the large substitution effect that occurred in 2012.

Since the price change (3 per cent) applies to the price of all retail prescription drugs (about $20.7 billion), it means that $621 million was being saved (without markups and dispensing fees) through lower sticker prices and the purchase of generics in 2015.

Innovative drugs represented about 34 per cent of patented drug sales, and patented drugs represented 59 per cent of all prescription drugs. So, over the two years of CSP, about $249 million in savings would be foregone ($621 million x 34 per cent x 59 per cent x two years).

This is significantly smaller than the estimate above of $392 million, but it is more short term and thus remains comparable.

Appendix B: Key Factors Impacting on Estimated Costs

The Canadian market for pharmaceuticals has been changing rapidly, both as a result of public policy, and as a result of new technologies and expiring patents. Those developments will affect future costs, and thus will also affect the impact of CSPs.

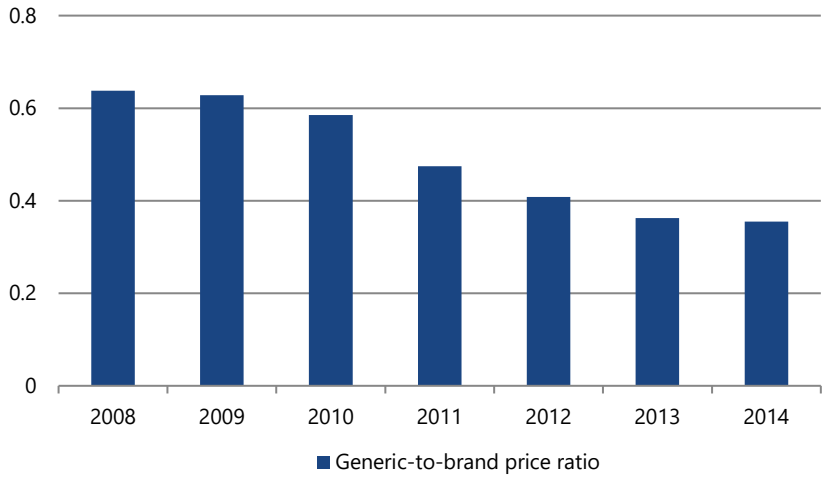
This appendix discusses how some of those factors have evolved over the recent past, and may change in the future.

B.1 Increasing Influence of Generics

Provincial health policy has been an important driver of drug-expenditure savings for Canadian consumers. It now generally requires the use of generic medicines whenever they are available (see Table C1 in NPDUIS, 2016). It also dictates the price of a generic medicine, sometimes with reference to the number of generics available.[26]

Those provincial policies have led to an increasing gap in pair-wise comparisons between generics and brand-name drugs. (Figure B-1). This has implications for the estimated cost of CSPs: the greater the price difference between generic drugs and their out-of-patent reference product, the larger is the cost of CSPs.

Figure B-1 The relative cost of generic medicine



Sources: NPDUIS, 2016.

Note: These ratios reflect all generic drugs (including those in public and private plans, as well as those purchased out-of-pocket). NPDUIS (2018) reports that the ratio in 2015Q4 and 2016Q4 was little changed from annual value for 2014.

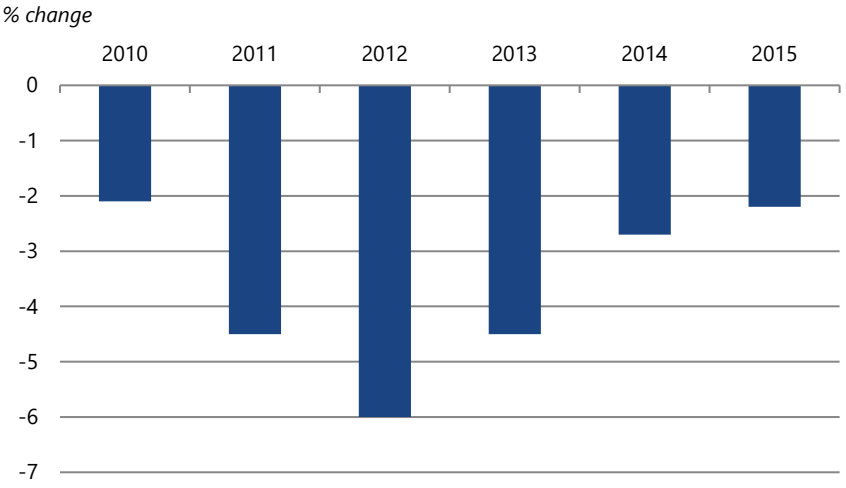
What is particularly germane about Figure B-1 is that the downward trend implies that a point estimate of the additional cost from the CSP would be misleading. Assuming that the price of the brand-name drug remained unchanged, between 2009 and 2014 the discount for generic drugs – when available – doubled. So, the cost of CSP in 2014 would have been significantly larger than in 2009.

Most recently, the price gap between brand-name and generics has not been growing as rapidly as it did after 2009. Contributing to that slowing change may be the waning effects of an event termed the patent cliff (Industry Canada, 2013).

In the years before, and during, 2012, a number of high-value drugs came off patent and their generic equivalents moved into the market. Indeed, the expiration of high-value patents would necessarily draw in generic equivalents (Chart 1 of Competition Bureau, 2007).

The combined effect of provincial changes and the patent cliff can be clearly discerned in the PMPRB data on private sector price changes due to generics. In 2012, the effects reached their maximum (Figure B-2), and have been declining since.

Figure B-2 Evidence of patent-cliff impacts and drug-policy changes from private drug plans



Sources: PMPRB, 2016.

Note: These changes combine both the price-change and generic-effects reported for the public sector in Figure A-1.

Since the patent cliff and provincial mandates were exceptional, the period around 2012 would bias estimates of the effect of CSP. The price change in 2015 was among the smallest of all the years illustrated for both private and public plans.

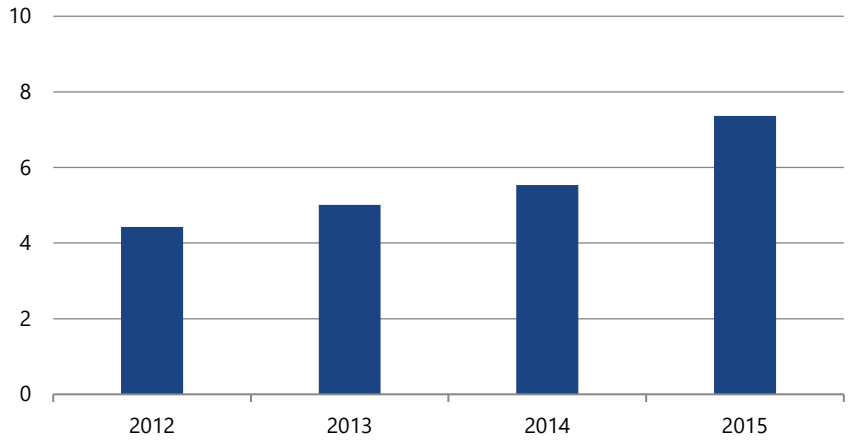
A related issue is that while the market share of patented drugs has fluctuated, in 2015 it was about the same as in 1999 and is close to a mean for the period 1999 to 2015 (PMPRB, 2015).

This latter observation suggests a contradiction that merits further comment. Generics have been impacting on drug costs (Figure 4-1). But the market share of patented drugs did not change much after 1999; in fact, it increased slightly. Those two observations can be reconciled if there was an increasing gap between the prices of patented and off-patent drugs.

Indeed, the relative price of patented versus non-patented drugs on average almost doubled over that time (Figure B-3). Part of the expanding difference in price is the introduction of newer more expensive drugs that treat maladies in more narrow populations.

Figure B-3 Ratio of patented to non-patented drug price

Ratio of relative prices



Sources: Canadian Institute of Health Information database, 2017.

Note: Data include only the public plans, and do not include Quebec. The data also excluded biological drugs; since the database did not distinguish between patented and non-patented biological drugs. The cost is per prescription, which can have a minor effect on the relative price since prescriptions for patented drugs tend to have fewer units. However, this would not by itself distort the change over time.

So, using the relative prices of patented drugs (of which innovative drugs are a component) and non-patented drugs in 2015 to estimate the cost of CSP would only provide a snapshot in a changing environment. The impact is even less clear when considering biosimilars; they tend to be expensive, which could lead to a flattening or partial reversal of the trend illustrated in Figure B-3.

B.2 Price Dynamic after Patent Expiration

Patented medicines in Canada are subject to price controls under PMPRB: it fixes prices with reference to an average of seven countries. Those prices are then allowed to rise at the rate of general inflation.

Once patent protection has ended, the drug is open to market competition. In traditional markets, the price of the off-patent product should fall as generics enter the market (see Conti and Berndt, 2017, who affirm that this is the case in the United States).

Surprisingly, in Canada the price of (popular) drugs losing patent tends to remain stable, with many brand-name manufacturers supplying the lower end of the market through authorised generics, or discounts directly to consumers (see PMPRB, 2015, page 16 for a discussion of Loyalty Cards).

For a sample of six popular drugs, though the price to consumers fell sharply (Table B-1), the brand-name drug continued to be listed in provincial formularies at the patented price; its retail price was unchanged. Since this occurs often, it must be more profitable for brand-name manufacturers to maintain the patented price than to lower it.

The reasons underlying that are not clear, but the use of brand-name drugs as a reference for the pricing of generics may contribute to it by removing some of the incentive for manufacturers to lower prices.

The speed at which the consumer cost of popular drugs falls can be rapid (Table B-1). For example, the patent for Crestor expired in 2012 and during the next five years, the volume and sales fell by about 80 per cent.

But since the price for the brand-name product is six times that of its generics, its sales value remained a robust $15 million roughly, relative to the generics.

Table B-1 **Payout change (%) for popular drugs on provincial formularies after patent expiration**

	ARICEPT	AVODAR	CELEBREX	CIPRALEX	CRESTOR	LYRICA
	5mg, 10mg	0.5mg	100mg, 200mg	10mg, 20mg	5 mg, 10mg, 20mg, 40mg	25mg, 50mg, 150mg, 300mg
2012	1	0	2	2	-13	1
2013	2	1	2	2	-68	-32
2014	-9	-4	1	0	-24	-55
2015	-24	-72	-34	-75	-9	-3
2016	7	-2	-57	-3	-1	0
Patent	*2013*	*2014*	*2014*	*2014*	*2012*	*2013*

Note: Canada-wide averages. Excludes Quebec, as well as institutions such as hospitals and care facilities. These reflect changes in the payments per prescription from public plans for each drug. In each case, the reference drug price did not change substantially.

The six-fold drop in provincial payouts per prescription when multiple generics enter the market is exceptional, but since it affects drugs of high value, it has a disproportionate impact on drug expenditures.

From 2011 to 2016, more than 500 patents expired. The total effect was to pull down the overall price index for drugs by about 25 per cent (implied from Figures A-1 and B-2). This was not sufficient to avoid an overall increase in drug expenditures as more expensive products came onto the market.

B.3 Biologics

A class of drugs known as *biological* products are isolated from natural sources such as human, animal or microorganism. In contrast to most drugs that are chemically synthesized (small molecule), biologics are complex (large molecule); they are not easily identified or characterized. Producing them is more difficult, and thus more expensive, since they are generally heat-sensitive and susceptible to microbial contamination

The process of approving generic-equivalents of biological drugs, or "biosimilars" requires more data than for generic small molecule drugs.

The cost to introduce a biosimilar is thus higher than it is with non-biological drugs both because the approval process is more expensive, but also because the production process is more demanding.

Looking forward, the breakthroughs achieved with biological drugs and their increasing use will make it challenging to achieve the same savings from expiring patents. In 2015, biological drugs reached 24 per cent of public drug plan expenditures (NPDUIS, 2017). This was almost double that of five years earlier.

In 2016, in public drug plans, non-patented biological drugs were about a third less expensive than patented biological drugs. This accords with the influence of biosimilars, even though only two were available with limited uptake: the price discount was about 40 per cent (infliximab and somatropin).

In Europe, the use of biosimilars is more wide spread with roughly 39 on the market. Nonetheless, savings there are generally less than 30 per cent (IQVIA, 2017). So, while there will be savings to be gained from patent expiration, they will not be as large as they currently are with small-molecule drugs if the trend toward biological (large-molecule) drugs continues.

Moreover, given the complexity and cost of developing a biosimilar, it is not always the case that one will be introduced. Somatuline, for example, had sales of $3.4 million when its last patent expired in 2015. In 2017, there were still no biosimilars, and its price had gone up by some 10 per cent. It was no longer under the purview of PMPRB so its price is no longer restricted.

These observations mean that the two years of CSP would not impact that segment of the market as strongly.

Appendix C: Data Issues

C.1 Caveat Regarding Cost

Although the data used in the analysis were comprehensive, they did not fully cover all Canadian expenditures on drugs. For 2015, PMPRB (2016) reported expenditures of $15.2 billion on patented medicines (61.8 per cent of all expenditures) and $9.4 billion on non-patented medicines (38.2 per cent).

The data available to PBO included $12 billion of expenditures for patented medicines, and $8.7 billion for non-patented medicines. So, $3.2 billion in patented and $1.3 billion in non-patented medicines were not included in PBO's datasets.

Most of the missing patented drugs were used in hospitals and other institutions, as were some of the non-patented drugs. To the extent that those omitted drugs were priced similarly to the included patented drugs, there would not be a bias in comparative costs.

For this report, the large samples of drugs in both the omitted and included groups should help to limit any bias: the average price of omitted drugs should approximate the average price of the included drugs (the law of large numbers).

Nonetheless, some understatement of the potential cost of CSP exists since the sample of medicines only represents about 75 per cent of expenditures in their respective categories.

If the proportion of the omitted patented medicines that were innovative was similar to the proportion in drugs that were included, then the estimated cost of CSP would be under-estimated by about one-third.

If hospitals and other institutions were disproportionately heavy users of innovative products, then the under-estimation would be higher.

Moreover, using the Register of Innovative Drugs may understate the drugs that will be eligible for CSPs, for example because new combinations of medicinal ingredients will be eligible for a CSP. A novel combination of previously approved medicinal ingredients can receive a CSP, even though the drug is not eligible for the data protection that is afforded drugs included in the Register of Innovative Drugs.

PBO estimates that including these factors would have increased the estimated cost of CSPs in 2015 by roughly 40 per cent, to about $557 million.

C.2 Shortcomings of Public Records

Entries in the Register of Innovative Drugs were used to identify DINs of marketed drugs by using the date of the NOC, the product name, and the medicinal ingredient. The patents underlying those DINs were then identified by using both the PMPRB (2016) list, as well as the Patent Register. In total, 295 DINs matched all three criteria.

To determine relative costs of innovative drugs, DINs would have to be identified for comparators: patented drugs, non-patented drugs and generics drugs. That task is challenging since Health Canada's Patent Register does not contain all drugs that are under patent protection.

Indeed, almost $700 million of drugs that are listed in PMPRB (2016) as coming under PMPRB's jurisdiction were listed in the Patent Register as having already had their patents expire.

Another $600 million or so were listed in PMPRB (2016), but were not included in the Patent Register at all.

Together those two groups represent a substantial omission from the Patent Register of drugs that are under patent protection. Though the patents are published by CIPO, they are treated there similarly to all other patented innovations – so there is less information than is typically provided through the Patent Register.

This is particularly noteworthy given that the purpose of the Patent Register is to both: (a) report patents for drugs that have received marketing authorization; and (b) require generic manufacturers to ensure they do not infringe any of those patents. But, as reported by Health Canada, inclusion in the patent list is voluntary:[27]

"*The submission of a 'patent list' is not obligatory. Therefore, even if a drug has received marketing authorization in Canada, patents may not be listed on the Patent Register for that drug.*"

So, addressing patents in the Patent Register effectively acts as a minimum requirement that a generic product must meet, but there may still be others that can block its market entry.

PBO was able to identify almost $1.3 billion in retail sales (at wholesale prices) of prescription patented drugs that were not included in the Patent Register in 2015.

Conversely, products that come under PMPRB jurisdiction are also somewhat limited. Roughly $1 billion in wholesale sales in 2015 were for products covered by a patent, but not under PMPRB's jurisdiction.

One reason for that is that PMPRB's mandate does not cover all types of patents related to medicinal products. For example, insulin products that are delivered by convenient patented devices "pens" are not under PMPRB's jurisdiction since the insulin itself is not patented.

This latter observation has the potential to significantly alter the proportion of expenditures by Canadians that are for patented pharmaceutical products. If the $1 billion were included in such expenditures, then for 2015 the proportion of products sold under patent would rise from 61.8 per cent as reported in PMPRB (2016) to 65.9 per cent. This would create a trend toward increasing expenditures for patented pharmaceutical products that is not currently seen in the data.

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Notes

1. Bill C-30, An Act to implement the Comprehensive Economic and Trade Agreement between Canada and the European Union and its Member States and to provide for certain other measures, 1st session, 42nd Parliament of Canada, 2016 (assented to 16 May 2017).
2. Another aspect of the CETA agreement that will delay availability of generic drugs is the change in the Right of Appeal: the right of patentees to challenge the entry of generics. At the time that this change was under public discussion, the government stated that its impact would be offset by providing a better process for generic manufacturers to substantiate their claims that patents had expired. This report does not look into that issue, and therefore may miss a source of additional cost – to the extent it exists.
3. Government of Canada, Technical Summary of Final Negotiated Outcomes, Canada-European Union Comprehensive Economic and Trade Agreement. Agreement-in Principle. October 18, 2013.
4. Based on Health Canada's Register of Innovative Drugs. If that proportion of innovative drugs also applies to patented medications used in hospitals and other institutions, then the pool of drugs for which a generic (cheaper) version will be delayed is about $5.2 billion (2015-based).
5. In the main text, an observation is made that there are factors to make the Register of Innovative Drugs a mild under-estimate of drugs that would be eligible for patent restoration (CSP).
6. Though for popular drugs the price declines little, if at all, after patent expiration. See discussion around Table B-1 in Appendix B.
7. *Food and Drug Regulations*, C.R.C., c. 870, at C.08.004.1(1)
8. Indeed, it is often the case that even the wider sample in the trials is not sufficiently large to identify all the issues surrounding its use, so analysis is continued even after the NOC is granted. In rare cases, the drugs have been withdrawn after widespread use identified risks that are deemed unacceptable.
9. A generic manufacturer can also claim that the patent was not valid, or that its product does not infringe on existing patents.
10. Health Canada, Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html
11. Submissions made after the six-year period, but before the end of the eight-year period will be placed on "Intellectual Property (IP) Hold". Health Canada, Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-

submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html

12. Some observers have noted that this locking-in prevents future policy changes regarding data protection since the law will be linked to a treaty. So, changing policy would require changes to CETA, which could involve renegotiation.

13. A similar provision had also been negotiated into the Trans-Pacific Partnership (TPP), so this is something that Canada's trading partners were targeting.

14. New medicinal ingredients that take longer than five years to obtain market approval will be eligible for a CSP. Grootendorst and Hollis (2011) found that for all drugs they examined, a 2-year patent extension would apply. Moreover, other studies (e.g. Grabowski and Vernon, 2000) have found that on average, it took 8 years to get market approval. Finally, patents that are added after the initial one covering the medicinal ingredient are less likely to be an obstacle for generic manufacturers.

15. See Certificate of Supplementary Protection Regulations, 2017, *Canada Gazette*, Vol. 151, No. 28, July 15, 2017.

16. http://www.pmprb-cepmb.gc.ca/CMFiles/Publications/Annual%20Reports/2014/2014_Annual_Report_Final_EN.pdf page 38 (price effect in graphic) says range of 38% to 16%. The Canadian Institute of Health Information (CIHI) data below shows by province, and the range is 35% to 18%. (Year of reference varies). https://secure.cihi.ca/free_products/NPDUIS_PlanInformationComparison2015_EN-web.pdf page 47.

17. http://www.theglobeandmail.com/news/british-columbia/federal-government-promises-compensation-over-eu-drug-costs-bc-minister/article14941457/, accessed June 1 2016; Government of Canada, Technical Summary of Final Negotiated Outcomes, Canada-European Union Comprehensive Economic and Trade Agreement. Agreement-in Principle. October 18, 2013.

18. The federal government does have some direct spending on drugs for some populations. In the twelve-month period preceding July 2015 this was estimated to be $645 million. (source: PBO calculations from CIHI (2016)). These populations include First Nations and Inuit persons, Veterans, members of the military, members of the Royal Canadian Mounted Police, refugees, and inmates in federal penitentiaries.

    In particular, First Nations and Inuit persons' drug expenses are covered by the federal Non-Insured Health Benefits (NIHB) Program. The NIHB is a national program that provides coverage to registered First Nations and recognized Inuit for a specified range of medically necessary items and services that are not covered by other plans and programs.

    Bill S-3 *An Act to amend the Indian Act* will result in an increase in the number of Canadians eligible for NIHB, thus increasing direct federal spending. This report does not provide an estimate for the interaction between Bill S-3 and CETA.

19. Pollack, A. (2015). "Drug Goes From $13.50 a Tablet to $750, Overnight". New York Times, September 20, 2015.

20. NPDUIS (2018) reported that brand-name drugs were 2 times as expensive as generic drugs in a side-by-side comparison. This was for a substantial sample of generic and brand-name drugs after the patent had expired. The same comparison using the data underlying Figure B-1 also gives the result that, on average, brand-name non-patented drugs are 2 times more expensive than generic drugs (per prescription).
21. NPDUIS (2018) estimates that on average brand-name drugs are 2 times as expensive as generics in a side-by-side comparison. That is, a comparison between brand-name and generic drugs for brand-name drugs that had a generic on the market. But for drugs whose sales are modest, it is not possible to make such a comparison if generics are not available. A broader comparison of brand-name versus generics in NPDUIS (2018) finds that brand-name drugs are, on average, 7 times more expensive than generic drugs.
22. Discount factor = [1 – (1/17)] * 100. The ratio of 1/17 reflects the relative price of a non-patented drug to a patented and innovative drug. That is, patented innovative drugs were 17 times more expensive than a non-patented drug.
23. When biologics are excluded and the ratio becomes 15, the discount factor falls to 93 percent. The cost estimate is only changed by a relatively small amount.
24. The change in the right of appeal has not been factored into the PBO results – though the government claims that other changes muted the effect of that change.
25. See Appendix B (particularly Figure B-1) for more discussion.
26. Not all drugs that lose patent protection are overwhelmed by the entry of generics. Whether and how many generics enter is dependent on the sales volume (see Chart 1 in Competition Bureau, 2007). Indeed, Ontario's schedule for what it will pay for a generic drug depends on how many of them are available – the more that are available, the less it will pay.
27. From https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/patent-register/frequently-asked-questions.html#a5