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The impact of the Canada – United States – Mexico Agreement on prescription drug expenditures in Canada

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

This report estimates the additional pharmacy-dispensed prescription drug expenditures for Canadian consumers that would result from the Canada-United States-Mexico Agreement (CUSMA). A two-year extension of data protection for biologics will delay the introduction of biosimilars for some expensive drugs. This would likely keep prices higher than they otherwise would have been.

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Executive Summary

The Canada-United States-Mexico Agreement (CUSMA) provides an extension to the term of protection for data resulting from drug trials. The extension applies to a category of pharmaceuticals known as innovative biologics. These are drugs with complex structures that have become increasingly popular. In recent years, pharmaceutical companies have been seeking extensions to the terms of data protection for such biologics to bolster the market exclusivity given by patents.

The CUSMA extends the term of data protection from eight years to 10 years. Only biologic drugs whose primary patent provides less than 10 years of market exclusivity would benefit from the change.

This report focuses on the potential cost of the extended term of data protection. It defines that cost as the additional expenditures on originator prescription biologics relative to their potential competitors. These are known as biosimilars, that is, alternative products that are less expensive.

To understand the underlying reason for the change, PBO reviewed the development time for innovative drugs, that is, the time between patent filing and market approval. This is the period during which extensive testing and drug trials occur. These are expensive, so denying competitors access to the data from tests and trials is an effective barrier to their market entry.

We found little difference in development time between biologic and non-biologic prescription drugs over recent years. This implies that the development time has been, on average, the same for these two types of drugs. Therefore, the primary motivation for the CUSMA change must be an apparent vulnerability in the patent protection of biologics.

Since the increased expenditures caused by the CUSMA will not begin until well into the future, PBO examines what the cost would have been in a hypothetical case, where the policy would have been in place in 2015.

However, an analysis of the market for biologics must consider how rapidly that market is evolving, in particular when it comes to the market for biosimilars. Europe's longer experience with biosimilars suggests considerable potential for their future use in Canada; indeed, there are signs of a recent increase in the uptake of biosimilars in Canada. We, therefore, base the cost estimate on a more widespread use of biosimilars, similar to that of Europe.

In 2015, some 16 biologics worth $422.4 million in prescription sales had data protection expiring between 2015 and 2023. By 2023, all drugs with data

protection in 2015 would have lost it without the CUSMA. On average, $52.8 million worth of sales would have lost data protection annually over that period ($422.4 million divided by eight years).

Effectively, for those drugs whose primary patent expires before the extended data protection, the CUSMA would have delayed the entry of lower-cost biosimilars that would have competed for market share. PBO assumed that the discount from a biosimilar would be 30 per cent and that biosimilars would affect sales in 75 per cent of the market of these biologics losing data protection. Both assumptions rely on experience from existing biosimilars in Canada and elsewhere, such as the European Union.

As a result of the delay, the annual average increase in drug costs would amount to $11.9 million per year. Doubling this number to account for the fact that it is a two-year extension produces an annual average increase in costs of $23.8 million between 2015 and 2023.

A secondary illustrative analysis in this report projects drug expenditures and CUSMA-induced costs into the future, namely 2028[1]. This is the year in which additional expenditures would first occur if ratification and implementation of CUSMA were completed by 2020.

This future analysis is motivated by two factors. One is the industry's concern that technological developments may render data protection to be the primary source of market exclusivity, rather than patent protection. The other is that biologics have been, and are likely to continue to be, gaining market share for pharmaceuticals.

Changing the underlying assumptions to account for both, PBO estimates that the CUSMA-induced increase in expenditures for consumers and drug plans would amount to at least $169 million in 2029, increasing annually thereafter.

If instead patent protection remains the primary source of market exclusivity even for biologics, then there would be little additional cost for consumers and drug plans attributable to the CUSMA.

1. Introduction

The Canada-United States-Mexico Agreement (CUSMA) was signed by Canada and its partners on November 30, 2018. While the agreement has garnered much attention for the changes it is expected to bring to the auto and dairy sectors, other provisions of the agreement will also have important impacts on other sectors of the economy. Intellectual property and digital commerce are areas where negotiators sought rules favourable to their industries for services that were not as important in the early 1990s.

Prior to the CUSMA, data protection was given to innovative drugs for a period of eight years[2,3]. The CUSMA extends data protection to 10 years, but only for a subset of drugs known as biologics – large-molecule drugs. This report focuses on the potential cost of those additional two years of data protection.

The extension of data protection will assure drug manufacturers have a minimum period of market exclusivity by delaying the introduction of lower cost alternatives, or biosimilars. These are drugs that achieve substantially similar outcomes, even though their molecular structures are not identical.

The beneficiaries will be drugs whose market exclusivity would have otherwise been less than 10 years. Whether market exclusivity is short because the time between patenting and marketing is longer for biologics, or patent workarounds are easier for biologics, or even because patents are challenged in court, is not relevant for the analysis here.[4] Though a review by PBO found little difference in the time between patenting and marketing for innovative biologics vis-a-vis other innovative drugs.

For the analysis undertaken in this report, we define the additional cost of the CUSMA change as the difference between the cost of originator drugs and their biosimilars. The originator is the reference drug that has market exclusivity, and the biosimilar is the potential competitor. The cost is calculated over the two-year period of the CUSMA extension.

Given arguments made by the pharmaceutical industry, as well as some recent legal decisions in the United States and Europe, this analysis uses the primary patent to denote the period of market exclusivity. The primary patent was the first to outline the drug's structure. That is, it is the earliest patent associated with a given drug.

The period of market exclusivity in Canada for originator biologics has been long (Lexchin, 2017) as there are currently few biosimilars available. However, we conjecture that this will change. Canada's use of generics, and Europe's wider adoption and positive experience with biosimilars, support that

conjecture. Other countries have also adopted biosimilars more widely (Appendix B).

For Canada, the proposed change must be implemented within five years after ratification. (The US Congress has yet to ratify the agreement.) PBO assumes it will only apply to new drugs introduced after implementation.[5] The additional expenditures could thus be eight years away, possibly even 13. However, some ambiguity in the language of the signed agreement (Article 20.10) could require Canada to apply it sooner.

Since the effects of the CUSMA will occur in the future, we chose to examine what the additional average annual expenditures would have been during 2015 to 2023. This is for the hypothetical case that the policy being in place from June 2014 to June 2015 (Section 3), but with availability of biosimilars similar to Europe's. The analysis illustrates the magnitude of the change.

We estimate that of $1.26 billion in prescription sales of biologics with data protection in 2014/15, some $422.4 million would have benefitted from extended data protection. Those drugs with data protection in 2015 would have had it expire over the period 2015 to 2023. So, on average, about $52.8 million in annual sales after 2015 would potentially be shielded from competition for up to two additional years – a delay caused by CUSMA.

After accounting for lower prices for biosimilars, as well as their likely market share (both based on European averages), PBO's estimate is that consumers and drug plans would have paid about $23.8 million more annually because of that delay.[6]

For completeness, PBO also undertook a longer-term cost analysis for 2028 based on projections of national drug expenditures for that year (Section 4). The year 2028 is the first in which extended data protection is projected to be effective. With biologics continuing to gain market share, we project that roughly $3.0 billion in annual sales of biologics could have data protection, which would then benefit from the two-year extension.

Given the rapidly evolving technology for developing and manufacturing biologics and the industry's concern regarding the weakness of patent protection, this longer-term estimate illustrates the cost exposure that the CUSMA has created. That is, if data protection becomes the primary source of market exclusivity for all innovative biologics, then the risk is that all biologics with data protection could cause additional expenditures. In that case, PBO estimates that by 2029, these additional expenditures would amount to $169 million, and would rise annually thereafter.

At the other extreme, the additional data protection may not provide much additional market exclusivity beyond what patent protection already does.

Finally, since extended data protection will only be relevant to biologics whose patents give them less than 10 years of market exclusivity, it is

effectively a backstop. However, this report does not deal with the issue of whether a 10-year minimum is necessary, that is, socially beneficial.

2. Background

2.1. Data Protection

Data protection prohibits the use by others of data required from the originator to obtain market approval of the safety and efficacy of a drug. That is, in the filing for a follow-on drug (generic or biosimilar)[7], the follow-on manufacturer can use the originator's data from previous trials, instead of doing their own trials, to obtain quicker market approval.

Since the trials that lead to market approval often cost hundreds of millions of dollars, and take time to complete, the savings in time and expenses are substantial. Preventing follow-on manufacturers from using the originator's data is, therefore, an effective barrier to potential competitors, even if the patent has expired.

Data protection is thus distinct from patent protection. It is only applicable on market approval, called notice of compliance, or NOC, for a new *innovative* drug.[8] Only about one in five new drugs approved for marketing meet the criteria of innovative drug.

Patent protection is fixed at 20 years[9] and begins on filing of the patent, which can be between five and 15 years before market approval is obtained. The patent can also be challenged in court. Therefore, the effective market exclusivity period conferred by patent protection varies from drug to drug.

In comparison, data protection is for a fixed amount of time (eight years prior to the CUSMA) and is not subject to court challenges. Given this particularity, it sometimes extends beyond primary patent expiration.

For example, in 2015, 16 of the biological drugs that were listed in Health Canada's Register of Innovative Drugs would have had their primary patent expire before the end of data protection. This effectively means that the two-year extension of data protection given in the CUSMA would have provided those drugs with up to two years of additional market exclusivity (Table 2-1).

Table 2-1 Prescription biologic drugs under data (and patent) protection in 2014/15

	Data protection ending - current	Data protection ending – with extension	Primary patent expiration (Canadian patent number)
Aflibercept	2021	2023	2020 (2376379)
Liraglutide	2018	2020	2017 (2264243)
Denosumab	2018	2020	2017 (2274987)
Abatacept	2014	2016	2012 (2110518)
Tocilizumab	2018	2020	2015 (2201781)
Eculizumab	2017	2019	2015 (2189015)
Belimumab	2019	2021	2021 (2407910)
Vedolizumab	2023	2025	2016 (2212702)
Collagenase Clostridium Histolyticum	2020	2022	2020 (2308842)
Pertuzumab	2021	2023	2020 (2376596)
Trastuzumab Emtansine	2021	2023	2020 (2370466)
Dulaglutide	2023	2025	2024 (2528591)
Ramucirumab	2023	2025	2023 (2478169)
Peginterferon Beta-1A	2023	2025	2019 (2345138)
Ocriplasmin	2021	2023	2020 (2389337)
Brentuximab Vedotin	2021	2023	2021 (2430135)

Sources: Parliamentary Budget Office, Health Canada's Patent Register, Health Canada's Register of Innovative Drugs, Health Canada's Notice of Compliance database.

Note: Drugs potentially affected if CUSMA had been in place in 2015. Each drug listed had sales between June 2014 and June 2015. For drugs that had been listed in Health Canada's Register of Innovative prior to 2016. The date for patent end represents PBO's assessment of the first patent that reported the drug's structure.

An early study of the time between the filing of a drug's patent and market approval found that the gap was longer for biologic drugs than for non-biologics (Grabowski, 2007). PBO followed up on that study by surveying some 77 biologics and 209 non-biologic drugs that were newly listed on Health Canada's Register of Innovative Drugs between 2006 and 2018 (and were listed in the Patent Register).

There was no statistically significant difference across the two groups in the mean times between the date of primary patent filing and the marketing date (both were about 11 years).

But both groups had a gradual upward trend from 2012 to 2018. To minimise any bias the upward trend may cause, we focused on the period between 2015 and 2018. Four years were judged necessary to minimise any small sample bias, while also avoiding effects of the gradual upward trend.

For drugs that received a notice of compliance in 2015 and after, the mean time to market approval was 144.2 months for biologics and 143.6 months

for non-biologics. Again, the difference between them was not statistically significant. Since it does not appear that biologics are taking longer to develop, this implies that the primary motivation for extending data protection for biologics was a concern regarding competitors circumventing patents.

While the link between drug costs and intellectual property protections remains contentious (see Box 2-1 for some observations), this report does not further consider that issue. It will focus solely on reporting on the magnitude of additional expenditures expected from the CUSMA.

Box 2-1. The cost of developing a new drug

An often-cited source to quantify the costs for developing a new drug is the Tufts University Center for the Study of Drug Development. They estimate the average cost for a new successful drug at between US$2.6 billion and $2.9 billion (2013 dollars; DiMasi, Brabowski and Hansen, 2016).

There are two schools of thought on those estimates. One is that those costs are high, and thus justify high drug prices. Some criticism on that view has focused on the outsized role of the cost of capital in the estimate which can amount to about half of the total. We note that their cost of capital is constant even though risk is declining substantially as development progresses.

The other is that R&D costs are "sunk" and thus should have no bearing on drug prices. This view also has its criticism since, as is much the case with oil exploration, an investor, no matter who it is, needs to anticipate a return from the outset. This would incorporate the possibility of failure, as well as periods of market exclusivity given by legal frameworks (e.g. intellectual property law).

Put differently, the value of a patent is determined by the anticipated income that it can generate with market exclusivity. R&D represents risky expenditures to obtain that patent (e.g., Hall, Thoma and Torrisi, 2004).

Public health policy also plays a role. Two recent changes in the United States led to larger markets for drugs. One was the expansion of coverage in the *Medicare Modernization Act* of 2003 to include drugs for seniors; the other was the expansion of Medicaid in 2010 as part of the *Affordable Care Act* (Frank and Ginsburg, 2017).

Box 2-1. The cost of developing a new drug (continued)

Those changes increased the likelihood that expensive treatments would be covered by public insurance plans. Indeed, recovering high R&D expenses was made even more likely when, in the Medicare expansion, government was: (a) prohibited from acting as a single buyer, and (b) prohibited from removing coverage of many drugs. Both neutralised its market power to negotiate lower prices.

A public and private insurance structure that places no limits on the cost of an effective life-saving treatment before inclusion on a formulary will provide additional incentives to increase R&D expenditures to find new and effective life-saving drugs.

Whether the estimates of DiMasi, Brabowski and Hansen (2016) are accurate is thus less an issue since R&D expenditures would be increasing in response to that market opening. In essence, the causality is the reverse of common perceptions; companies spend more on R&D *because* there is a large and profitable market where they have significant control over prices.

Indeed, in 2016, some 6,300 trials of new drugs were underway (Long, 2017). Of these, 74 per cent were for innovative medicinal compounds, that is, those that have no relationship to any previously on the market. If, as some have suggested (Frank and Ginsburg, 2017), the compounds that are relatively easy to find and manufacture have mostly been found, those drugs in development will necessarily be more expensive, for both biologics and other drugs.

Illustrating that process is the influx of venture capital into drug development, which amounted to more than $12 billion in 2017 in the United States (Venture Monitor, 2018). Given the nature of venture capital, this signals an expectation that new and innovative products will earn high returns. Again, whether that return is socially justified is beyond the scope of this report.

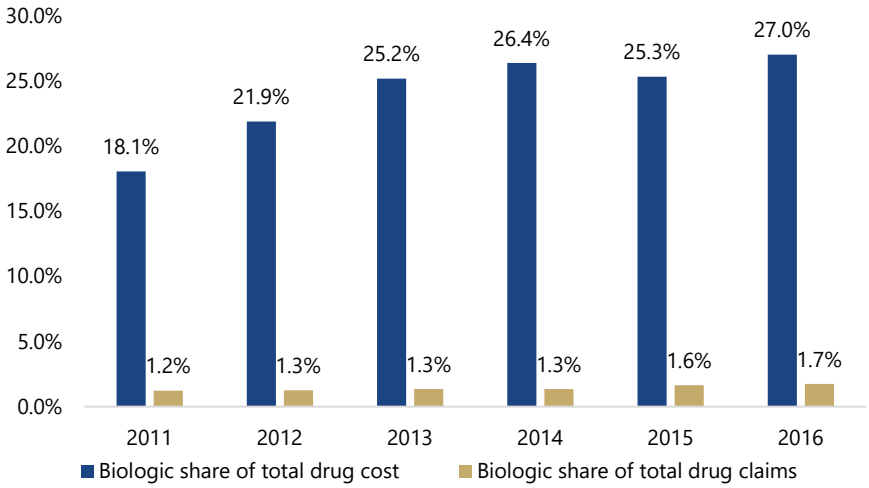
2.2. Biologics in the Canadian pharmaceutical market

From 2010-11 to 2016-17, total expenditure on drugs in provincial publicly-administered drug plans rose from $6.5 billion to $7.8 billion, an increase of almost 20 per cent (this does not include expenditures in Quebec, hospitals or institutions – including those drugs taken at home, or dispensing fees and markups).

Nearly 73 per cent of this increase in expenditure can be attributed to biological drugs. Their market share of total sales increased from 18 per cent to 27 per cent during the same period (Figure 2-1). As of 2016-17,

$2.12 billion were spent on biologics in provincial public plans, and $4.8 billion in Canada as a whole.

Figure 2-1 **Prescription drugs under data (and patent) protection in 2015**



Source: Parliamentary Budget Officer using data from NPDUIS Database

Note: Not including public expenditures in : hospitals and institutions, Quebec

The increase in expenditures on biologics comes primarily from their increased use rather than from an influx of new drugs. Indeed, as Table 2-2 shows, average expenditures per biological drug increased by more than half from 2010-11 to 2016-17.

The increase in expenditures also does not come from an increase in the prices of existing drugs. The relative cost per prescription of biologics compared to other patented medicines fell mildly between 2011 and 2016. In 2011 the ratio of their costs was 8.4, and in 2016 it was lower at 6.6[10].

So, the change in expenditures on biologics, compared to other patented medicines, largely moved in step with the relative change in prescriptions. That is, the share of prescriptions for biologics went up by roughly half, from 1.2 per cent of all prescriptions to 1.7 per cent (Figure 2-1); the share of expenditures on biologics also went up by roughly half, from 18.1 per cent to 27.0 per cent.

Behind the outsized share in expenditures is the price per prescription of biologics. They are more expensive as a whole than other brand-name drugs, as evidenced in the provincial drug plans (Table 2-2).

Table 2-2 Public plan spending on biologics and non-biologics

	Price per prescription		Average expenditure per drug	
	2010/11	**2016/17**	**2010/11**	**2016/17**
Biologics	$439	$459	$20M	$31.1M
Other brand name	$53	$70	$4.6M	$5.9M*

Source: Parliamentary Budget Officer using data from NPDUIS Database

Note: Not including public expenditures in : hospitals and institutions, Quebec

*Extrapolated by PBO

These trends suggest that biologics will continue to be important sources of treatment for Canadians, as well as major sources of expenditures. The change made in the CUSMA is thus potentially important.

2.3. Underlying drivers

For the analysis undertaken in this report, we define the additional cost of the CUSMA change as the difference between the cost for Canadians of an originator prescription drug and its potential competitor, a biosimilar, over the two-year period of the CUSMA extension. More specifically, we focus on biologic drugs that are innovative, which is a legally well-defined concept, and whose primary patent will expire before extended data protection ends.

PBO's use of the primary patent is based on a judgement that most of the follow-on patents are process or other specific patents, which have been less of an obstacle to the introduction of biosimilars (Adair, 2016). This argument has been made forcefully by the industry in the United States[11].

In addition, the analysis assumes that Canada will move toward European levels of biosimilar availability by the time the first drugs with extended data protection lose it, that is, in 2028. This means that, by value, we will assume that about 75 per cent of the market for biologics losing data protection will have their retail price affected by biosimilars. This means that these biologics will either become cheaper or they will be replaced by cheaper biosimilars once they become available.

Underlying that assumption is Canada's position vis-à-vis the European Union regarding generics. There are more generics currently used in Canada than there are in many European countries, even though Europeans generally use more biosimilars. If studies of the European experience continue to show similar outcomes between biosimilars and their originator drugs (e.g., Wiland, et al, 2017; La Noce and Ernst, 2018), Canada is more likely to follow suit.

Moreover, Canada only recently finalised the framework for allowing biosimilars onto the market (though first allowed as of 2010, an updated

guidance was issued in 2016). The European Medicines Agency has had a framework for the entry of biosimilars since 2005. The first approval came in 2006.

One can find some indications of Canada's opening to biosimilars in the provincial formularies. For example, since February 2017, the Province of Quebec stopped reimbursing Remicade (Infliximab) for a large segment of the affected population, reimbursing its biosimilar instead.

The same thing happened for Lantus (Insulin Glargine) in August 2017 and Enbrel (Etanercept) in January 2018. These are three of the top selling biologics; such a change in an insurance policy should have a significant impact on the uptake of biosimilars.

This does not necessarily imply that most biologics will be followed by a biosimilar. As with small-molecule generic drugs, it is mainly the most expensive ones (by treatment) that will have biosimilars (see Competition Bureau, 2006, and Lexchin, 2017, for generic drugs).

So roughly one-fifth of biologics whose patent expires before data protection will have a biosimilar, or about one in 10 of all biologics with data protection. But these biologics will account for a large market share.[12]

Since the effects of the CUSMA will be felt well into an unpredictable future, our primary analytical tool is to examine what the average annual additional cost would have been had the policy had been in place in 2015. That is, the additional expenditures during 2015 to 2023 for drugs that had data protection and were sold between June 2014 and June 2015.

The eight-year period after 2015 ensures that all biologics with data protection would have lost it. It also avoids dependence on a single year's loss of data protection that could be anomalous[13]. It is thus an illustrative analysis to outline the magnitude of the change. There were 18 biologics during that time out of 38 whose patent was due to expire before the end of an extended data protection period (Table 2-1).

3. Incremental expenditures: CUSMA

For the period June, 2014 to June, 2015, some $422.4 million in prescription sales (net of dispensing fees and markups) could have benefited from the CUSMA (Table 3-2). Since data protection on those drugs would have expired over the following eight years, 2015 to 2023, this means an average annual expiration on $52.8 million worth of sales.

From this value, the magnitude of the impact from CUSMA can be conditionally estimated. That is, it can answer the hypothetical question: *if the policy were in place in 2015, what would have been the additional expenditures between 2015 and 2023 (annual average)?*

Table 3-1 Expenditures on data-protected prescription biologics

Millions of dollars	**Sales 2014/15 – Total Canada**
Innovative biologics with primary patent ending before data protection	
Aflibercept	108.1
Liraglutide	92.0
Denosumab	82.3
Abatacept	58.9
Tocilizumab	38.6
Eculizumab	26.9
Belimumab	4.0
Vedolizumab	3.4
Collagenase Clostridium Histolyticum	2.3
Pertuzumab	1.7
Trastuzumab Emtansine	1.4
Dulaglutide	1.0
Ramucirumab	0.7
Peginterferon Beta-1A	0.6
Ocriplasmin	0.4
Brentuximab Vedotin	0.1
TOTAL	**422.4**
Innovative biologics with primary patent ending after data protection	
Ranibizumab; Ustekinumab; Golimumab; Certolizumab Pegol; Natalizumab; Vaccine Hpv Type 6,11,16,18; Velaglucerase Alfa; Alglucosidase Alfa; Secukinumab; Romiplostim; Vaccine,Pneumococcal Conjugate; Vaccine, Neisseria Meningitidis; Canakinumab; Pembrolizumab; Evolocumab; Mepolizumab; Vaccine, Rotavirus; Nivolumab; Alirocumab; Meningococcal Polysaccharide Vac; Panitumumab; Elosulfase Alfa; Idursulfase.	
TOTAL	**806.3**

Sources: Parliamentary Budget Officer and IQVIA

Notes: Net of dispensing fees and markups. Not including non-prescription drugs.

For drugs that had been listed in Health Canada's Register of Innovative Drugs prior to 2016. The date for patent end represents PBO's assessment of the first patent that reported the drug's structure.

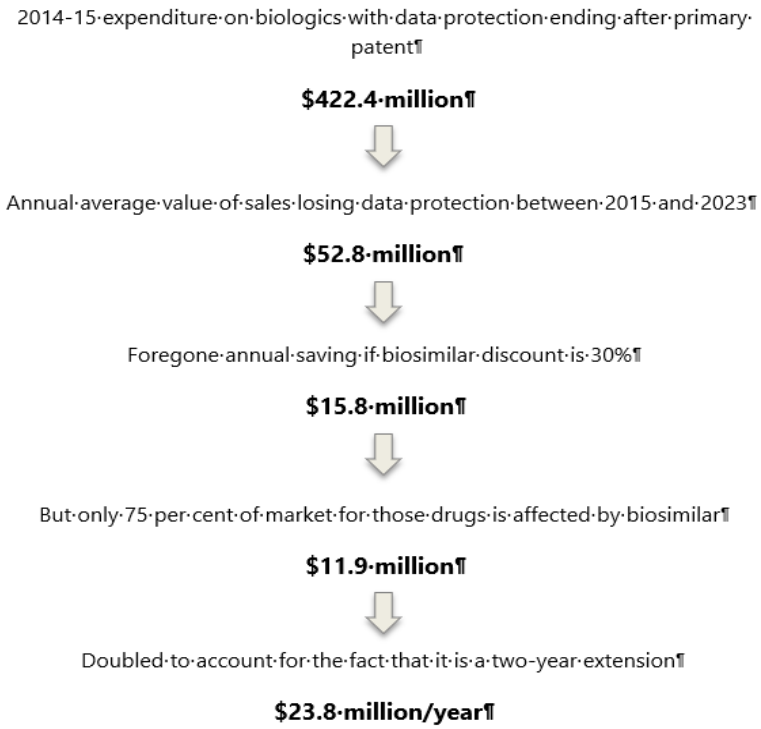
Between 2015 and 2023, some $1.26 billion in 2014-15 sales of biologics would lose data protection, or $157 million per year on average.

We base our cost estimate on a more widespread use of biosimilars than was actually the case in 2014-15. This is because we conjecture that Canada will move towards Europeans level of biosimilar availability by the time the CUSMA will cause increased expenditures.

Using a 30 per cent discount for biosimilars, that level of $52.8 million in expenditures should fall to $37.0 million, or $15.8 million less (Figure 3-2 provides an illustration). Since that discount is unlikely to apply to all drugs losing data protection (not all will have competition from a biosimilar), the additional expenditures caused by the CUSMA should be reduced further.

We project that about 75 per cent of the value of biologics losing data protection will be influenced by biosimilars. More precisely, 75 per cent of the market by value will experience a 30 per cent discount. This combines price adjustments in originator drugs, as seen in Europe, with lower prices for biosimilars. The additional expenditures caused by the CUSMA thus decline to $11.9 million per year. Doubling this number to account for the two year extension gives an annual cost of $23.8 million [14].

Figure 3-2 CUSMA-induced expenditures (2015-based)



Appendix A outlines the impact of assumptions regarding pricing through a sensitivity analysis.

This $23.8 million in additional annual expenditures is an under-estimate since it does not account for non-prescription patented drugs, that is, those used primarily in hospitals or institutions. In 2015, this represented some $3.1 billion in expenditures on patented medicines, or about one-fifth of the total.

This is an area where considerable progress is being made in developing new treatments (immunotherapies) and pharmaceutical companies are investing heavily. Biologics in particular are used in treating cancer (oncology), but oncology drugs are mostly non-prescription, and therefore do not appear in our dataset[15].

As a result, there is a downward bias in our estimate presented above as well as the estimate that will be presented below. Data limitations prevented PBO from quantifying it.

3.1. Caveats : growing markets and biosimilar availability

There are two particularly important caveats to the foregoing estimate. The first is that since it is based on 2014-15 sales, it would understate future expenditures, given the growing market for, and share of, biologics. The second is that it assumes that biosimilars will be considerably more pervasive in Canada than they were in 2015. This would tend to overstate the CUSMA's incremental expenditures if biosimilars turn out to be less available.

However, we believe both assumptions are strong. Regarding the first, the market for biologics is growing rapidly and the pipeline of future drugs is long. Regarding the second, the pipeline for biosimilars is also long. Potential biosimilars are already in use in other countries (Appendix B). Canada's use of generics has been historically high, led by a drive for cost-containment in provinces that may extend to biosimilars if Europe's success with them continues.

Indeed, cost-containment in Europe has led in some countries to biosimilars being the drug of first choice, though in Canada whether a biologic or biosimilar is used often remains the doctor's choice, though Ontario and Quebec have taken some step to influence that choice.

Both these caveats have significant impacts; the first would lead to an understated impact of the CUSMA change, while the second would lead to an overstatement if it did not materialize. So, the estimate of $23.8 million (in 2015 dollars) per year might remain the product of opposing forces in the future. The next sections examine these two factors more carefully.

Growth in expenditures on biologics

The above analysis outlined the incremental cost due to the CUSMA *as if* it had existed in 2015. This section discusses why using 2015 for the analysis would lead to an understatement of future costs. It outlines upward pressures on those costs due to the increasing number of drug therapies and their rising cost.

To that end, PBO constructed a central scenario for expenditures on biologics that projects yearly national growth at 8.2 per cent to 2028. This is based on an average of growth rates over the past three years (see Patented Medicine Prices Review Board, 2018). At that rate, spending on prescription biologics is expected to reach $13.1 billion in 2028 (Table 3-2), up from $4.7 billion in 2014-15.

These projections are reported in nominal dollars. Given the very low rate of past inflation of pharmaceuticals, they are identical to real dollars if past trends continue (Box 3-1). Indeed, what this implies is that the historical growth rates on which we base our projections are actually *real* growth rates.

Box 3-1. Price inflation in pharmaceuticals

Statistics Canada has reported an index for Medicinal Products and Pharmaceuticals since 1978 (see their Table 18-10-0004-13). This is a sub-component of the Consumer Price Index.

Initially the index increased rapidly along with other prices in the economy. But that changed in 2002, after which it remained essentially flat. This implies that, as a whole, price increases since 2002 have been associated with "quality" improvements.

Side-stepping the difficult issue of measuring quality improvements in pharmaceuticals (see Bosworth, et al, 2018, for a discussion), if that process continues, it will have important consequences. One is that while PBO-projected real incomes might increase by 19 per cent to 2028, real expenditures on prescription pharmaceuticals would increase by 57 per cent. So an increasing share of the economy is going to medicinal products and pharmaceuticals.

For this report, the main importance of very low price-inflation for pharmaceuticals is that the nominal expenditures projected for 2028 would be very similar to real expenditures. As a result, there is no distinction made between the two measures.

Total expenditures on prescription pharmaceuticals in 2028 will reach $34.5 billion. This is conservative if we compare it to the long-term projection just for *patented* medicines developed by Health Canada, about $26 billion in 2028 (Government of Canada, 2017)[16].

At the provincial level, the growth rate for spending on biologics was just over 12 per cent between 2011 and 2016. But a more detailed look reveals that it was skewed. That is, in the years from 2011 to 2016, expenditures on biologics in provincial plans initially grew by well over 15 per cent, but then fell to almost half that rate (7.9 per cent) by 2016.

Table 3-2 Projected growth in spending

	Expenditures on biologics – 2028 ($billions)	Expenditures on brand name – 2028 ($billions)	Expenditures on generics – 2028 ($billions)	Market share for biologics – 2028	Year-on-year growth parameters		
					Biologic	Brand-name	Generic
Baseline - National	**13.1**	**13.1**	**8.1**	**38.0%**	8.2%	2.4%	2.6%
Baseline - Provincial	**5.4**	**4.7**	**2.8**	**42.1%**	8.2%	2.4%	2.6%

Source: Parliamentary Budget Officer using data from NPDUIS database,

Notes: Not including public expenditures in : hospitals and institutions and drugs from those soruces taken at home.

This baseline scenario projects a substantial shift in drug expenditure towards biologics. Fully 64 per cent of the projected increase in spending in the provincial plans will come from biologics (at the national level, the projected increase is 60 per cent). This is still lower than the 73 per cent gain that occurred between 2011 and 2016, but we project spending on biologics to maintain the pace of the last three years.

Further slowing is not projected in the central scenario, given two factors: the pipeline for biologics, and the observation that between 2015 and 2017, about one-third of new innovative drugs were biologics, suggesting their market share should increase.

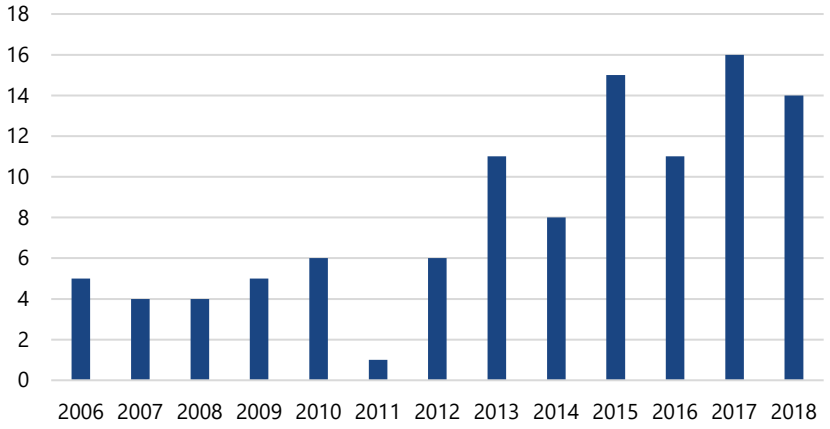
Nonetheless, this recent slowing of expenditure growth creates some uncertainty that calls for outlining alternative scenarios. Further uncertainty in the growth of brand-name drug expenditures also merits a closer look[17]. Variations in those two growth rates characterize alternative scenarios (outlined in Appendix A).

Additional perspectives on the baseline also come from: (1) the increasing number of biologics receiving data protection (Figure 3-3), and (2) the pipeline and market entry of new biologics.

Regarding the first, consistent with what has been happening in other jurisdictions, more innovative biologics have been coming to market. While

this does not by itself assure increasing expenditures, it nonetheless suggests a source of pressure to do so.

Figure 3-3 Number of biologics receiving data protection



Source: Health Canada's Register of Innovative Drugs.

Regarding the second, the number of incoming biologics is important. In their 2017 edition of Meds Entry Watch, PMPRB found that in 2017, 19 drugs received market approval *and* registered sales in Canada. Of these 19 drugs, 10 were biologics (PMPRB, 2019, Table C1). In 2016, six out of the 15 drugs that received market approval *and* subsequently registered sales in Canada were biologics (PMPRB, 2019, Table B1).

In addition, in the 2016 edition of the PMPRB Pipeline Monitor (PMPRB, 2016), which gives an overview of the drugs that are likely to enter the Canadian market soon, nine drugs out of 27 were also biologics. Given that, in 2015-16, barely 11 per cent of all drugs that registered sales in Canada were biologics, it seems like the shift towards biologics will continue.

The impact of biosimilars

The analysis using 2015 as the base year assumed a wider availability of biosimilars in the future. Failure to meet that objective over-estimate incremental costs.

This sub-section will provide some underpinning for PBO's projected use of biosimilars in Canada. It is based on Canada's experience with generics, and the more widespread use of biosimilars in Europe and elsewhere (see Appendix B for an international comparison).

Biosimilars are around 15 per cent cheaper than the reference drug in international markets, but on average are more than 30 per cent cheaper in Canada (Table 3-3)[18]. This is smaller than the discount typical of generic

small-molecule drugs, but is not likely to change much given the cost of developing and manufacturing biologics.

Table 3-3 Biosimilars discount in Canada and elsewhere

	Infliximab	Filgrastim	Insulin Glargine	Etanercept
Ref. drug name	Remicade	Neupogen	Lantus	Enbrel
Biosimilar name	Inflectra - Renflexis	Grastofil	Basaglar	Brenzys – Erelzi
Biosimilar discount– Quebec/Ontario formularies	46%	17%	24%	34%
Biosimilar discount – PMPRB7	13%	11%	16%	18%
Biosimilar discount – OECD	17%	17%	13%	14%
Market value of the reference drug – Total Canada 2015 ($millions)	926	93	269	332
Market value of the reference drug – Public plans 2015-16 ($millions)	367	45	128	151

Sources: Parliamentary Budget Officer, IQVIA, and PMPRB (Meds Entry Watch 2017)

Canada's currently small uptake in units of biosimilars (43.5 per cent for Filgrastim, but 4 per cent or less for Infliximab, Insulin Glargine and Etanercept) is contrasted by the experience in other countries. In Norway, Denmark and Finland for instance, Infliximab biosimilars reduced sales of Remicade by more than 90 per cent.

Even in cases where the biosimilar is less dominant in European countries, the originator drug may have lowered its price to forestall or compete with a biosimilar (e.g. Megerlin et al, 2013).

For other drugs (Epoetin, Filgrastim and Somatropin), similar outcomes have occurred when biosimilars entered the market as facilitated by national policy (Morton, Stern and Stern, 2016). In those cases, the market shares of biosimilars for Epoetin, Filgrastim and Somatropin reached 37 per cent, 28 per cent and 30 per cent, respectively, in 2014.

The difference that a regulatory framework can make is illustrated in the wide divergence of their availability in various countries (see Appendix B). In Europe, by mid-2018, about 50 biosimilars had been approved for 16 molecules.

Europe began to encourage biosimilars at an early stage and facilitated their entry through clear rules. But even within the European Union, differences in implementation at the national level have led to substantial differences in the use of biosimilars (Moorkens, et al, 2017). Studies show that in countries

where the government has been active in educating patients and promoting biosimilars, their uptake is significantly higher (Rezumata, et al, 2017).

The cost of the CUSMA is thus intrinsically linked to Canada's future use of biosimilars. The more pervasive the use of biosimilars is in Canada, the higher the cost in missed savings.

4. A longer-term estimate of costs

The preceding sections estimated the additional expenditures for biologics *as if* extended data protection had been in place in 2015. This section looks more speculatively at a scenario in 2028 that is based on extending current trends in drug expenditures.

The year 2028 is germane because the precedent with the Comprehensive Economic and Trade Agreement (CETA) between Canada and the European Union suggests that extended data protection will apply only to drugs not yet on the market. If ratification of CUSMA occurs during 2019, and implementation in 2020, then 2028 is the date at which the additional expenditures would begin.

The baseline outlined in Table 3-2 projected that Canada-wide expenditures for biologics could reach $13.1 billion in 2028. To estimate the proportion that will be under data protection, we turn to provincial data for 2011 to 2016 (Table 4-1). There, an average of 23 per cent of biologics by value were under data protection.

Table 4-1 Sales of biologics under data protection – Provincial public plans

	Total sales of biologics ($billions)	Sales of biologics under data protection ($millions)	Proportion of sales for biologics under data protection	Number of drugs under data protection
2011	1.26	287	23%	12
2012	1.51	390	26%	12
2013	1.79	525	29%	13
2014	1.94	580	30%	13
2015	2.09	299	14%	12
2016	2.25	389	17%	11
			Average : 23%	

Source: Parliamentary Budget Officer using data from NPDUIS database

Note: Data protection was introduced in 2006, so 2014 is the first year in which drugs could lose it under the eight-year rule. The sharp drop in 2015 is due to Ranibizumab, a drug with more than $200 million in sales, losing data protection that year.

The significant fluctuations from year to year in the sale of drugs under data protection underscore that any estimate is approximate. The steep drop in 2015 was caused by a single drug (Ranibizumab) with $200 million in sales to provincial plans. So, for the analysis here, we use average over the six years. On average, 23 per cent of biologics were under data protection.

At the national level for all prescriptions, for which PBO only has data for 2014-15, the proportion under data protection during that period was 27 per cent. This is higher than the provincial average (23 per cent; Table 4-1). The national number would be much closer to the provincial number without Ranibizumab, which lost data protection midway through 2015.

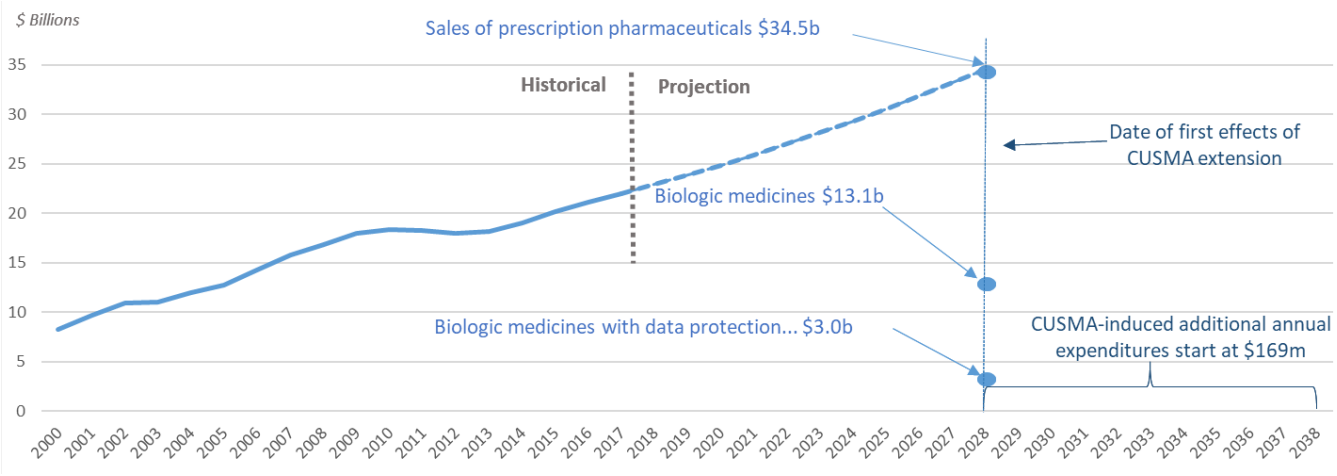
Combining a 23 per cent proportion with the projection of $13.1 billion implies that $3.0 billion could be spent on biologics under data protection in 2028 (nationally). This does not include drugs provided in hospitals and institutions.

This projection is, of course, sensitive to various assumed growth rates, as outlined in Appendix A. An even more profound uncertainty relates to the future pace of technological developments.

The economic incentives to develop profitable biologics may keep pushing manufacturers into drugs that are either more costly and time-consuming to approve, or more subject to patent workarounds. This could make data protection the primary source of market exclusivity. Since it was an industry-led push that extended data protection in the United States, it is a scenario worth exploring further.

If data protection becomes the dominant source of market exclusivity, then the CUSMA-induced additional expenditures would be for all biologics receiving the extension. Since above we projected that that would be roughly $3.0 billion in 2028, then in the subsequent years, the additional expenditures would start at $169 million, and rise thereafter (Figure 4-1).

Figure 4-1 Long-term projection



Source: Parliamentary Budget Officer using data from PMPRB (2018b)

Note: The $169 million is an average cost based on drugs under data protection in 2028 (those granted it between 2020 and 2028). This average eight-year cost will rise each year after 2029 as a new eight-year historical average becomes effective.

Does not include drugs used in hospitals and institutions. Data prior to 2015 are included for completeness, and are backcasted to grow at the same rate as PMPRB-reported expenditures that include hospitals and institutions.

On the other hand, if future developments leave patents as the primary source of market exclusivity, then the CUSMA will have little additional impact.

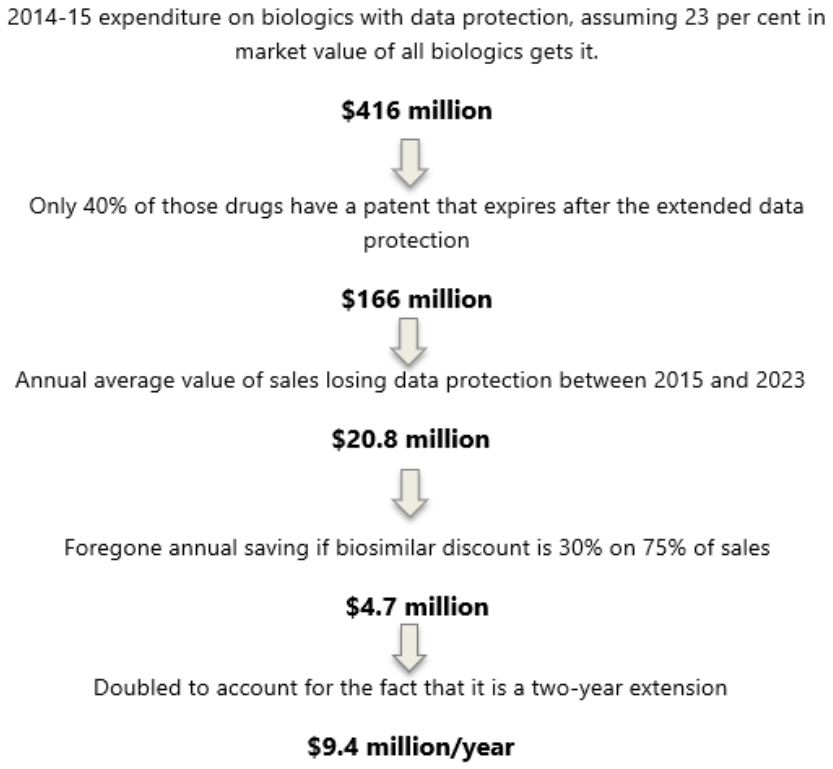
5. Provincial estimates

In the preceding sections, PBO estimated national costs using both a retrospective analysis *as if* the policy had been in place in 2015, and a prospective analysis where the importance of data protection would change by 2028.

This section calculates the part of those estimated retrospective and prospective costs that would be borne by provincial public drug plans.

For the retrospective scenario, provincial plans (not including Quebec) would have had to pay an additional $9.4 million annually based on drugs with data protection in 2015 (Figure 5-1). This result uses some of the same assumptions of the national estimate, that is, that the discount for biosimilars is 30 per cent, and it affects 75 per cent of the market for the drugs that lose data protection.

Figure 5-1 CUSMA-caused provincial expenditures (2015)



For a prospective analysis that looks at 2028, we project that provincial plans will cover some $5.4 billion in prescription biologics (Table 3-2). Of this, some $1.2 billion will be under data protection (using the 23 per cent proportion of Table 4-1).

In the subsequent years (after 2028), the additional CUSMA-induced expenditures by provincial plans would start at $70 million and rise annually thereafter. Again, this is only for the case in which data protection becomes the dominant source of market exclusivity.

6. Other Factors

The high number of biological products in advanced development, and their traditionally high average cost, suggest a baseline with increasing expenditures. Indeed, by some estimates, venture capital firms poured over US$12 billion into biotech companies in 2017 (Venture Monitor, 2018), so the sector is attracting substantial speculative investments.

The potential impact of the CUSMA on those rising expenditures is sensitive to how drug development for biologics evolves globally. While there are currently only a few cases where data protection would extend market exclusivity, significantly more drugs could be impacted in the future. This creates an exposure to additional drug expenditures that we estimated at the high end to start at $169 million annually from 2029.

However, the overall cost of the CUSMA extension estimated above should be put into context with other recent and proposed changes to drug pricing in Canada. The CETA agreement extended patent-like protection for an additional two years to all innovative drugs. In an earlier report, PBO estimated that had the change been in place for drugs listed as innovative in 2015, it would have led to $392 million per year in additional expenditures on prescription drugs.

However, an even more important series of changes have been proposed by the federal government that would have an impact on all patented medicines (Government of Canada, 2017). They are due to come into force in June 2019, though delays are putting the timeline in doubt.

Under regulations implementing the *Patent Act*, (Patented Medicines Regulations, SOR/94-688) patented drug manufacturers must set the price in Canada to be an average of prices in seven countries (including the United States). The Patent Medicine Prices Review Board (PMPRB) oversees and enforces drug pricing for patents in Canada. In response to rapid price increases in the United States, Health Canada has proposed dropping the United States from that list and extending the group of countries to 12. It also proposed changes in: (1) the criteria affecting those prices, and (2) requiring firms to report discounts they are giving for their products elsewhere.

Health Canada estimates that it would save some $0.22 billion in the first year (2019) of those changes. By 2028, a decade later, the savings would rise to $2.78 billion (in 2017 dollars). The average annual reduction is $1.2 billion, or some 40 per cent of the increase in expenditures on patented drugs that it projects for 2028.

A comparison of the three changes proposed by Health Canada for the PMPRB with the recent changes resulting from the trade agreements (CUSMA and CETA) suggests that those concerning the PMPRB will dominate (Table 6-1)[19]. That is, there will be a large net reduction in expenditures.

Table 6-1 Comparison of recent policy change: impact on annual pharmaceutical expenditures

	Expenditure impact in 2015 ($ million)	Expenditure impact, annual average 2019 to 2028 ($ million, 2017)
PBO Estimates		
CUSMA	+23.8*	
CETA	+392	
PMPRB proposed regulations		
Reference countries		-397
New pricing factors		-536
Price discounts		-287

Sources: Parliamentary Budget Officer and Government of Canada (2017)

* With considerable future uncertainty due to technological developments

Note: CUSMA and CETA estimates are by PBO. PMPRB regulatory impacts are by Health Canada. For additional detail concerning the estimates and regulatory changes, see Government of Canada, 2017.

Since each of the policy changes (CUSMA, CETA and the three PMPRB regulations) is permanent, they affect annual expenditures indefinitely and will accumulate.

Appendix A: Sensitivity Analysis

A.1 Cost of data protection extension - 2015

In the cost estimate presented in Figure 3-2 (main text), we assumed that the discount from biosimilars would be 30 per cent and that it would affect sales in 75 per cent of biologics losing data protection. Both assumptions rely on experience from existing biosimilars in Canada and elsewhere, such as the European Union.

However, there are large variations within European Union countries and across different drug classes. This prompts a review in a sensitivity analysis by changing those assumptions.

Research on the subject suggests that biosimilar discounts are usually between 15 and 30 per cent (e.g. Rémuzata et al, 2017). Although Table 3-3 showed that, in Canada, the discount seems to be in the upper end of that range, data from other countries show that it could be closer to 15 per cent. We thus show in Table A-1 below what the cost of data protection extension would be if the discount were 15 per cent.

Also uncertain is the assumption that the discount will affect 75 per cent of sales (either by switching to biosimilars, or by price reduction of the reference drug to compete with biosimilars). Among other factors, in Scandinavian countries, active promotion of biosimilars by governments has led to their largely displacing the originator drugs.

Countries without such policies tended to have lower penetration of biosimilars. The uncertainty caused by that, and other factors, leads to some interest in exploring the importance to the results of alternative market penetrations (Table A-1).

Table A-1 Alternative scenarios for the 2015 cost estimate

	Scenario 1	Scenario 2	Scenario 3 (baseline)	Scenario 4
Market value before biosimilar entry ($million)	52.8	52.8	**52.8**	52.8
Biosimilar discount	15%	15%	**30%**	30%
Market penetration of biosimilar	25%	50%	**75%**	100%
Annual cost of 2 year extension ($million)	4	7.9	**23.8**	31.7

Source: Parliamentary Budget Officer

A.2 Alternative growth scenarios

The baseline scenario presented in Table 3-2 is based on growth rates of: (1) 8.2 per cent for biological drugs, (2) 2.4 per cent for non-biological brand name, and (3) 2.6 per cent for generics. These are based on past trends as well as what appears to be in the drug pipeline. Since there is considerable uncertainty surrounding these projections, we provide three alternative scenarios with different growth rates.

Regarding biologics, the annual growth rate of the past 10 years leads to some concern that 8.2 per cent growth might be an underestimation. An alternative is the annual growth of the past five years, 12.4 per cent.

On the other hand, the annual growth rate has been decreasing somewhat steadily in the past 10 years and it could keep on decreasing. Therefore, illustrating the impact of an annual growth rate of 4 per cent would be an informative alternative.

For non-biological brand-name drugs, the annual average growth rate of 2.4 per cent is heavily impacted by growth in 2015 (22 per cent). This is mainly the result of Direct Acting Anti-Viral drugs (DAAs) entering the market.

If we exclude DAAs, the average annual growth of expenditures for non-biological brand-name drugs would be close to zero over the past five years (partially the influence of more widespread use of generics). We will, therefore, use a zero-growth rate for these drugs as another scenario. [20]

The results with these alternative growth rates create a significant range for expenditures on biologics (Table A-2). By themselves, they would increase the cost of the CUSMA change by 57 per cent or lower it by 74 per cent.

Table A-2 Projected growth in spending – National plans

	Expenditures on biologics – 2028 ($billions)	Expenditures on brand name – 2028 ($billions)	Expenditures on generics – 2028 ($billions)	Market share for biologics – 2028	Year-on-year growth parameters		
					Biologic	Brand-name	Generic
Alternative 1	21.6	13.1	8.1	49%	12.4%	2.4%	2.6%
Alternative 2	13.1	9.7	8.1	42.2%	8.2%	0%	2.6%
Alternative 3	7.9	9.7	8.1	31%	4%	0%	2.6%

Source: Parliamentary Budget Officer

We can construct a comparison of these scenarios to Health Canada's projected growth for patented medicines (Government of Canada, 2017). That is, since historical expenditures on patented medicines only changed moderately in comparison to expenditures on all medicines, their projection can be scaled up to cover all prescription drugs, and then scaled down to remove non-prescription drugs.

Whereas Health Canada's scenario implies an average growth rate of about 3.9 per cent to 2028, PBO's is 4.2 per cent (for all drugs). So, Health Canada's scenario is a little below PBO's central case, but it remains between Alternatives 1 and 2 (Table A.2), which have overall growth rates of 6 per cent and 3.4 per cent, respectively.

For the CUSMA-induced additional costs, by 2029 they would be between $101 million and $279 million and rising (Alternative 1 versus Alternative 3, respectively).

A.3 Alternative scenarios – growth, and market penetration of biosimilars

We now extend the alternative growth scenarios of the previous sub-sections to include alternative discounts and market penetration for biosimilars. The low-end scenarios will feature a 15 per cent discount, with 25 per cent of the market being affected by that discount, and 4 per cent annual average growth for biologics.

The high-end scenario will feature a 30 per cent discount with 100 per cent of the market affected, and a 12.4 per cent annual average growth rate for biologics. The range created is effectively one that leads to little effect from the CUSMA change, to roughly a doubling of the central scenario presented in the main text.

Table A-3 Sensitivity analysis for the long-term cost estimate

	Annual cost in 2029 ($millions)
High Scenario	372
Low Scenario	16.9

Source: Parliamentary Budget Officer

The estimates from Table A-3 rely on two additional assumptions: a fixed proportion of biologicals under data protection (23 per cent), and that by 2028, data protection will be the main source of market exclusivity for innovative drugs. The high end of cost ($372 million annually) represents a low-likelihood potential exposure that CUSMA has created for drug expenditures in Canada.

As outlined earlier, if patent protection instead remains the main source of market exclusivity, then the effect of an additional two years of data protection will be in the lower end of our sensitivity analysis.

Appendix B: Biosimilar availability

Table B-1 Biosimilar availability by country

Active substance	Canada	Japan	USA	EU	India	Active substance	Canada	Japan	USA	EU	India
Abatacept	·	·	·	·	·	Insulin (human)	·	·	·	·	·
Abciximab	·	·	·	·	Y	Insulin (pork)	·	·	·	·	·
Adalimumab	·	·	Y	Y	Y	Insulin aspart	·	·	·	·	·
Aflibercept	·	·	·	·	·	Insulin detemir	·	·	·	·	·
Agalsidase alfa	·	·	·	·	·	Insulin glargine	·	Y	Y	Y	Y
Alemtuzumab	·	·	·	·	·	Insulin glulisine	·	·	·	·	·
Allergen extracts	·	·	·	·	·	Insulin lispro	·	·	Y	Y	·
Alteplase	·	·	·	·	·	Interferon alfa-2b	·	·	·	·	Y
Anakinra	·	·	·	·	·	Interferon beta-1a	·	·	·	·	Y
Basiliximab	·	·	·	·	·	Interferon beta-1b	·	·	·	·	·
Bcg vaccine	·	·	·	·	·	Laronidase	·	·	·	·	·
Becaplermin	·	·	·	·	·	Liraglutide	·	·	·	·	·
Bevacizumab	·	·	Y	Y	Y	Multienzymes (lipase, protease etc)	·	·	·	·	·
Botulinum toxin	·	·	·	·	·	Nadroparin	·	·	·	·	·
Certolizumab pegol	·	·	·	·	·	Natalizumab	·	·	·	·	·
Chorionic gonadotrophin hormone r-hcg	·	·	·	·	Y	Ocriplasmin	·	·	·	·	·
Collagenase	·	·	·	·	·	Omalizumab	·	·	·	·	·
Dalteparin	·	·	·	·	·	Pegfilgrastim	Y	·	Y	Y	Y
Danaparoid	·	·	·	·	·	Pegylated recombinant interferon alfa	·	·	·	·	Y
Darbepoetin alfa	·	Y	·	·	Y	Peginterferon alfa-2a, combinations	·	·	·	·	·
Denosumab	·	·	·	·	·	Pegvisomant	·	·	·	·	·
Dornase alfa (desoxyribonuclease)	·	·	·	·	·	Pneumococcus, purified polysacc.antigen	·	·	·	·	·
Eculizumab	·	·	·	·	·	Ranibizumab	·	·	·	·	Y
Enoxaparin sodium	·	·	·	Y	·	Rasburicase	·	·	·	·	Y
Epoetin alfa	·	Y	Y	Y	Y	Recombinant granulocytec (molgramostim)	·	·	·	·	Y
Etanercept	Y	Y	Y	Y	Y	Reteplase	·	·	·	·	·
Filgrastim	Y	Y	Y	Y	Y	Rh-PDGF-BB + β-TCP	·	·	·	·	Y
Follitropin alfa	·	·	·	Y	Y	Rituximab	·	Y	·	Y	Y
Follitropin beta	·	·	·	·	·	Secukinumab	·	·	·	·	·
Glucagon	·	·	·	·	·	Somatropin	Y	Y	·	Y	·
Golimumab	·	·	·	·	·	Streptokinase	·	·	·	·	Y
Grass pollen	·	·	·	·	·	Teriparatide	·	·	·	Y	Y
Heparin	·	·	·	·	·	Thyrotrophin	·	·	·	·	·
Hepatitis B vaccine	·	·	·	·	Y	Tinzaparin	·	·	·	·	·
Infliximab	Y	Y	Y	Y	Y	Tocilizumab	·	·	·	·	·
Influenza, inactivated, split	·	·	·	·	·	Trastuzumab	·	Y	Y	Y	Y
Influenza, inactivated, whole	·	·	·	·	·	Ustekinumab	·	·	·	·	·
Influenza, live attenuated	·	·	·	·	·						

Number of biological ingredients with biosimilars: Canada, 5; Japan, 9; USA, 10; EU, 15; India, 24.

Source: Generics and Biosimilars Initiative, http://gabionline.net (accessed November, 2018)

One reason for the higher prevalence of biosimilars in India is the more common rejection of follow-on patents in the country's intellectual property framework. Indeed, the *Indian Patents Act* has specific provisions (section 3(d)) against "evergreening" of patents through secondary filings.

The main takeaway from this observation is that there is significant potential for the introduction of biosimilars.

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Notes

1. If the precedent of patent-like protections – "patent restoration" – under the Canada-EU trade agreement is followed, then only new drugs introduced after ratification will benefit.
2. With an additional six months if tested for pediatric conditions.
3. The backdrop to the US request is an earlier change to US policy. Data protection for biologicals was extended as part of the *Affordable Care Act* of 2010. This was done in exchange for a clear regulatory framework that facilitated the entry and approval of biosimilars. In the years since its approval, extending data protection has become a touchstone of negotiations for new trade agreements (including the TPP and CUSMA).
4. Indeed, Mullard (2016) reviews industry studies that find that biologics are almost twice as likely as new small molecule drugs to move from initial clinical trials to market approval. This suggests that the approval process for biologics should, on average, be cheaper than for other new drugs.
5. This is similar to the implementation of "patent restoration" with the Canada-EU Comprehensive Economic and Trade Agreement (CETA). Only new drugs approved for marketing after the implementation of the agreement (September 2017) are eligible for extended patent-like protections.
6. The expenditure saving as reported from biosimilars is averaged over private and public insurance plans.
7. A follow-on drug is a drug whose molecular structure has been demonstrated to be close (functionally equivalent) or identical to the original drug.
8. Which are listed in Health Canada's Register of Innovative Drugs.
9. But can be extended to 22 years when a product is sufficiently innovative and took more than five years to be approved for marketing in Canada.
10. There was a steep increase in the price per prescription of non-biologics brand name in 2015. This is due to the entry of Direct Acting Anti-viral (DAA) drugs that treat Hepatitis C. These are expensive drugs that captured a large share of drug expenditures in a short period of time.
11. *Patent protection is often less robust for biologics than for small molecule drugs. Many biologic patents are process patents or relatively narrowly drawn product patents. These may be susceptible to work-arounds, especially under a regulatory regime that permits biosimilars to differ in their structural features from innovator products. Furthermore, if a biologic's development time is extended, there may be a very limited period of patent protection remaining once a product is approved. Given the increased potential for biologics patents to be "worked around" by biosimilar manufacturers making patents less certain, 12 years of data protection for biologics is needed (PhRMA, 2015).*

    PBO's use of the quote is not an endorsement. Its purpose is to underpin a scenario to be analysed quantitatively.

12. For 2015, the top four drugs (out of 18) accounted for about three-quarters of expenditures on biologics with data protection. It is not unusual that a small proportion of factors account for a large proportion of the effect. Indeed, it is so common that it has been dubbed the *Pareto Principle*, which posits that 80 per cent of the effect is cause by 20 per cent of the factors (the so-called 80/20 rule).

13. For example, Aflibercept, a drug with sales of over $200 million, will lose data protection in 2021. The cost of the CUSMA in this year will thus be relatively high. On the other hand, no biologics lost data protection in 2016. Therefore there would be no cost associated with the CUSMA for 2016. Using a 8-year period thus ensures that we paint a more accurate picture.

14. If we account for CETA, which would have extended patent protection by two additional years for innovative drugs, these numbers change slightly. The total sales of drugs under data protection falls to $430.3 million, but more significantly the additional period of market exclusivity given by the CUSMA would be shorter. Indeed, from two years that period would fall to an average per drug of 16 months (1.3 years). Therefore, accounting for the change brought by the CETA, the net cost of the CUSMA would be $16.6 million.

15. One illustrative example is Trastuzumab, used for certain types of breast cancer. In 2016, sales for this drug totalled $250 million in Canada (NPDUIS). This drug did not appear in our dataset because it is mainly used in hospitals. Although it is not currently under data protection, therefore not affecting our cost estimate, it shows that we are missing a non-trivial share of the market.

16. Assuming patented medicines remain a constant share of total spending of 62 per cent, Health Canada projections would imply total spending on drugs of about $41.4 billion by 2028. However, they do not report spending on biologics. Moreover, PBO's dataset does not include drugs used in hospitals and institutions.

17. The average growth over 2015 and 2016 may be skewed by the entry in 2015 of direct anti-viral drugs for hepatitis C. These are expensive drugs that captured a large share drug of expenditures in a short period of time. Indeed, without these drugs, growth in expenditure for non-biologic brand names in 2015 would have been almost zero.

18. This could be due to the fact in Canada the reference biologics have higher prevailing prices than in international markets.

19. A small upward adjustment to the estimate for the trade agreements (CUSMA and CETA) should be made to reflect the difference in base year vis-a-vis the PMPRB estimates. Nonetheless, the savings anticipated from the PMPRB change would still be much bigger than the costs caused by the trade agreements.

20. This latter scenario has weaker underpinnings than the others since it precludes major disruptive drug introductions. A drug that significantly slows dementia due to Alzheimer's would be one such drug. It remains the focus of intense research efforts given the potential market for a successful treatment.