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Independent Assessment of Health Canada's Cost-Benefit Analysis of the Impact of Proposed Amendments to the Patented Medicines Regulations (CG1)

By

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EXECUTIVE SUMMARY

Purpose of this report

On December 2nd, 2017 the Government of Canada published in the Canada Gazette (CG1) proposed regulations to amend the Patented Medicines Regulations. The proposed amendments would:

- Introduce new economics – based price regulatory factors to ensure that "prices reflect value and Canada's willingness and ability to pay for patented medicines".
- Update the schedule used by the PMPRB for international price comparisons to be better aligned with median OECD prices.
- Reduce some reporting obligations and set out new patentee informative reporting requirements.
- Require patentees to report prices and revenues net of all price adjustments.

The accompanying regulatory impact analysis statement (RIAS) included analysis of the costs and benefits of the proposed amendments which was based on the September 2017 Cost Benefit Analysis (CBA) carried out by the Strategic Policy Branch of Health Canada (3)[1].

The purpose of the present report is to provide an independent assessment of:

[1] Numbers in brackets refer to the documents listed at the end of our report.

First, whether the proposed new regulatory features are in keeping with considerations that are reasonable for the PMPRB to use in determining non- excessive price ceilings, responsive to market developments, and consistent with approaches used in other similar jurisdictions.

Second, whether the assumptions used and methodology employed by Health Canada in its CBA and by the industry in its Critical Appraisal are likely to produce reasonable estimates of costs and benefits of the proposed regulatory changes.

Third, whether all relevant impacts of the proposed changes have been considered.

Background

The PMPRB was created in 1987 to decide on the maximum non-excessive price at which holders of patents on medicines can sell their product in Canada. This system of providing monopoly pricing power to patent holders subject to a price ceiling determined by PMPRB aims to achieve an optimum balance between the twin objectives of encouraging innovation and protecting consumers against "excessive" pricing by monopoly providers of patented products.

The legal basis for PMPRB's regulatory role is the 1987 Patent Act in which subsection 85 (1) specifies, in general terms, the factors that the Board is supposed to take into account when deciding whether or not a price charged in Canada is excessive, including the prices of "other medicines in the same therapeutic class" in Canada, and the prices at which the medicine

has been sold "in other countries". The Act does not, however, provide further detail and also says that the Board can consider "such other factors as may be specified in any regulations made for the purposes of this subsection" (27).

The current proposals for reform only involve amending the current Patented Medicines Regulation by adding new economics-based factors, changing the list of countries to be used in international price comparisons, and changing the language describing what patentees must report to the PMPRB. Once these changes are gazetted, the PMPRB will consult with stakeholders and formulate a revised set of Guidelines to implement the new process.

The Amendments

In Chapter III, we consider the proposed Amendments to the Regulation in general terms. The proposed new regulatory economic factors include pharmacoeconomic valuation, "market size" (both in the sense of expected sales volume of a drug, and subsequent actual sales), and Canada's GDP in comparison with other countries. We think taking these factors into account is reasonable, and as we note in Appendix 1, Canada would follow the example of pharmaceutical purchasing and regulatory agencies in other countries by doing so. For example, pharmacoeconomic evaluation plays a major role in influencing drug prices in the UK and Australia, and agreements between agencies and pharmaceutical companies in Europe often include provisions under which prices depend on the volume of sales. We also think that it is reasonable to modify the list of countries that are used in price comparisons so that it excludes the US and includes new countries that have healthcare systems that are more like Canada's.

Finally, we think that the new reporting requirements are reasonable since confidential discounts have created a growing disparity between actual net transaction prices and list prices for drugs, both in Canada and elsewhere.

The Health Canada CBA: Underlying Assumptions

As the Department responsible for medicine price regulation, Health Canada is required by Treasury Board to prepare of Cost-Benefit Analysis of the proposed regulatory changes. It did so in 2017. A summary of the CBA was included as part of its CG1 submission; more detail is in a 38-page document that is available on request (2). The CBA was done with the assistance of PMPRB staff which possesses extensive expertise and data on the pharmaceutical industry, in Canada and internationally.

Our assessment (in Chapter IV) is that the baseline forecast of future industry revenues and the impact of proposed regulatory changes on those revenues, have been carefully done, and were done based on empirical analysis that made judicious use of recent data and on not unreasonable assumptions about the application of the new operating Guidelines that will be formulated and published after the final regulation changes are gazetted.

However, we were only able to reach this conclusion after careful review of a number of working documents, including decks (4 and 5) and computer files (6 and 7), many of which have not been made publicly available. It is our strong suggestion that when a new CBA is undertaken, to accompany the CG2 submission, there should be a full explanation of what these

assumptions were. Moreover, if there is to be a meaningful debate in the process of consultation about the way the Guidelines should be changed, new estimates should be provided by PMPRB to show how different Guideline provisions would affect the estimated impact of the new regulations.

The Health Canada CBA: The Net Benefit Calculation

As we observe in Chapter IV, we believe that the regulatory changes might well yield a net benefit to Canada. But estimating the precise size of that net benefit (or cost) is difficult because there is no well established methodology to do so. Among other things, the estimate requires making an assessment of the degree to which Canada is currently perceived as contributing its fair share to global R&D financing. If it is generally judged by our trading partners whose firms carry out R&D and benefit from Canadian patent protection that Canada already is contributing its fair share or more, then the cost of a dollar of patentee revenue lost could legitimately be assigned a lower weight than the benefit of a dollar saved by Canadian payers. In this situation, there can clearly be a net benefit to Canadians of reductions in ceilings on non- excessive prices as PMPRB implements the proposed regulations.

The CBA analysis of the aggregate impact of the new regulations indicates that there will be a significant reduction in pharmaceutical revenues and expenditures while at the same time allowing Canadian prices that are similar to the median prices in comparable jurisdictions. If other countries recognize this, they are less likely to engage in retaliatory measures that are

costly to us, making it more likely that the proposed regulatory changes will yield a net benefit to Canada[2].

While it may be reasonable to treat the value of a reduction in taxpayer-funded expenditure for drugs as somewhat greater than the value of a reduction the revenues of patent holders, in our view there is no reasonable justification for the large multiplier value of 4.3 that is used in the CBA calculation. Although there is very likely a net benefit from the application of the proposed regulations, it is entirely unreasonable to ascribe much credence to the calculated net present value benefit of $12.7 billion even though the estimated impacts on annual expenditures (gross benefits) and industry revenues (costs) were themselves not at all unreasonable. This estimate has been quoted in the public debate about pharmaceutical policy (HESA p.84) even though, in our judgment, there is virtually no theoretical or serious empirical support for the calculation that produced it. It is our sense that on balance it is appropriate at this time in Canada to weigh the lost revenues (i.e. costs) somewhat less than the savings to prayers (benefits).

The PDCI Re-analysis

In January 2018, following CG1 and HC's CBA becoming available, PDCI – Market Access Inc (PDCI) published a report (19) containing a critique of HC's analysis; the report is listed as being commissioned by IMC[3]. Part of it is devoted to what is referred to as a Re-

[2] See the discussion in the section on Calculating the Net Benefit to Canada in Chapter IV.
[3] This initial report was supplemented with a deck on July 5 called a Re-analysis (20). We have considered both documents in making our comments in the Chapter 5.

analysis of the predicted impact on the pharmaceutical industry of the proposals, and a critique of the methodology used to produce the estimated net benefit to Canada.

The PDCI calculations produced a much larger estimate of the reduction in pharmaceutical revenue that would result from the new regulations than in the HC CBA: In present value terms, it was put at $26.1 billion, whereas HC had a figure of $8.6 billion. Part of the reason for the difference arose from PDCI using a much lower discount rate in the calculation than HC (1.5% vs 7%), but the PDCI estimate remains more than twice as high as the HC one even if one uses the same discount rate.

While we appreciate the clarity and simplicity of the PDCI approach to estimating the impact of the change in the schedule from PMPRB7 to PMPRB12 on industry revenues from 2019 to 2028, our considered view is that this approach is likely to overestimate the actual nominal impact, at least if one assumes that the Guideline changes that would accompany the new Regulations were similar to those that were used in generating the CBA. Going forward, re-estimates should be made by PMPRB on the basis of differing scenarios for the implementation guidelines.

Conclusion

Everything considered, we judge that the introduction of the new factors, enhanced reporting requirements, and revisions of the schedule for international price comparisons is reasonable and that there is no good economic or conceptual reason not to proceed with the

proposed regulatory changes. In the analysis of the impact of the regulations which will be included with CGII, we strongly suggest that Health Canada, in the methodology paper that will accompany the analysis, make clear its precise assumptions about PMPRB's future implementation of the new regulations.

In the process of ongoing PMPRB consultations about the Guidelines to implement the new regulatory framework, we strongly suggest that the PMPRB fine tune the analysis of the impact of the proposed regulations using alternative ways to operationalize the new factors, the schedule, and the reporting requirements. With respect to the pharmacoeconomic value factor, we suggest that further analysis be done testing alternative threshold values. Cost utility analysis is in our view an appropriate tool for payers to use in establishing the maximum prices that they should be willing to pay on behalf of consumers, and it can also be helpful in deciding when a proposed price would be "excessive". However, as discussed in Chapter III, while there is widespread agreement that CUA can be used as a flexible tool in payer/supplier negotiations, there is less agreement on the adaptations required to use CUA as a tool in price regulation. In any case, the choice of threshold maximum costs per QALY is critical to implementation of this factor. Going forward it is very important that Guidelines set out how these thresholds are to be established and which other agencies (CADTH, INESSS, etc.) might be involved in providing the underlying analysis.

Giving the PMPRB a potentially more effective set of tools may be a valuable first step, but in the long run, achieving closer integration among the agencies that are involved in the drug pricing process may be more important for achieving a system that properly balances the

objectives of patient and payer protection against that of contributing Canada's fair share of global pharmaceutical R&D financing.

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CHAPTER I

INTRODUCTION

Background and Purpose of this report

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- Introduce a new economics – based price regulatory factors to ensure that "prices reflect value and Canada's willingness and ability to pay for patented medicines".
- Update the schedule used by the PMPRB for international price comparisons to be better aligned with median OECD prices.
- Reduce some reporting obligations and set out new patentee informative reporting requirements.
- Require patentees to report prices and revenues net of all price adjustments.

The accompanying regulatory impact analysis statement (RIAS) included analysis of the costs and benefits of the proposed amendments which was based on the September 2017 Cost Benefit Analysis (CBA) carried out by the Strategic Policy Branch of Health Canada (3).
Following the publication of the proposed amendments, Health Canada carried out consultations during which some stakeholders expressed concerns both with some features of the proposed

amendments and with the approach used in the department's CBA to arrive at estimates of the associated benefits and costs[4].

Purpose of this Report

The purpose of this report is to provide an independent assessment of:

First, whether the proposed new regulatory features are in keeping with considerations that are reasonable for the PMPRB to use in determining non- excessive price ceilings, responsive to market developments, and consistent with approaches used in other similar jurisdictions.

Second, whether the assumptions used and methodology employed by Health Canada in its CBA and by the industry in its Critical Appraisal are likely to produce reasonable estimates of costs and benefits of the proposed regulatory changes.

Third, whether all relevant impacts of the proposed changes have been considered.

The report concludes with a summary position on two issues: the use of the new features in the determination of non-excessive price ceilings, and second the reasonableness of the estimates of the direct quantitative impacts of the proposed amendments on prices of medicines

[4] See (8): proposed amendments to the Patented Medicines Regulations. See also (19): a critical appraisal of the cost benefits analysis: PDCI Markets Access, January 2018.

and revenues of patentees, taking into account uncertainties related to data, expected technological change, administrative guidelines and compliance issues.[5]

Outline of Report

Chapter II of this report provides basic background information and analysis of the factors affecting the pricing of medicines, including the role of the patent system to encourage pharmaceutical companies to innovate and develop new drugs, and the role of the PMPRB to help provide consumers with some protection against "excessive" prices for patented medicines. The chapter concludes with a short description of how the PMPRB has operated up to now in developing criteria for assessing whether prices may be "excessive", and of the criticism by consumers that current regulations and guidelines have not allowed the PMPRB to adequately protect consumers from excessively high prices of patented medicines.

Chapter III of the report first describes the changes in the regulations proposed by the government in December 2017 including: the three new factors to be considered by the PMPRB, the update of the comparator country schedule, and changes in price reporting obligations. The chapter provides an assessment of the theoretical rationale underlying each of the three new factors, including a note on cost utility analysis.

[5] See (2) Statement of work. We have assessed the reasonableness of the quantitative estimates contained in the CBA analysis (3) on the basis of the assumptions made about the implementation Guidelines in that analysis of September 8, 2017. In subsequent documents (15, 28), PMPRB suggests moving away from using discount information in the way assumed in the CBA analysis. We have not re-estimated the CBA analysis on the basis of those changing assumptions.

Chapter IV sets out our technical analysis of Health Canada empirical estimates of the costs and the benefits of the new approach as presented in Health Canada's Cost Benefit Analysis of September 2017. It provides an assessment of the reasonableness of both the baseline projection of revenues of the industry, and the impact of the proposed regulatory changes. The sensitivity of the estimates to changes in assumptions about future PMPRB Guidelines and other technical factors is also assessed.

Chapter V provides a similar assessment of the estimates in the Critical Appraisal provided by PDCI Market Access.

Chapter VI concludes with a summary assessment of both quantitative and qualitative net benefits of the proposed changes.

CHAPTER II

Patents, Innovation, and Prices: The Role of the PMPRB

Introduction

In order to protect consumers of patented pharmaceutical products from excessive prices while at the same time encouraging the development of innovative new products by providing a period of monopoly pricing power to patent holders, the PMPRB was created in 1987 to determine the maximum non-excessive price at which patent holders can sell their product in Canada. This system of providing monopoly pricing power to patent holders subject to a price ceiling determined by PMPRB aims to achieve an optimum balance between the twin objectives of encouraging innovation and protecting consumers against "excessive" pricing by monopoly providers of patented products.

In this section of this report, we provide first a description of and rationale for the patent system, then a description of the role of the PMPRB and its current method of determining maximum allowable medicine prices, and finally a summary of the criticisms of its current method of operation that have led the Government of Canada to propose (CG1) changes in the regulations applied by the PMPRB.

Innovation & Patent Protection

Canada's Patent Act, like corresponding laws in other countries, creates legal monopolies for patented products: once a patent is registered for a medicine or product, that medicine can only be legally sold in Canada by the patent owner, usually the company that has developed the drug, or by an entity that has obtained the patent owner's permission. Governments in OECD countries (through patent legislation) grant such monopoly protection because, in theory, such monopoly protection gives an incentive to individuals and firms to spend resources on R&D that result in socially valuable new technologies and medicines which generate net benefits for consumers that make use of them, even when new medicines are sold at high prices.

But as generations of economic students have learned, monopoly (a market where there is only a single seller) is typically inefficient because the per-unit price charged by a monopolist is likely to be higher than what it costs to produce additional units of the product. The inefficiency results because the high price makes buyers restrict the amounts of the product that they use so the amount that is sold and used is less than what it would be if other producers were allowed to sell it and its price was closer to what it costs to produce. The concept of economic efficiency in economic analysis is ultimately based on consideration of what is good for consumers, and in the aggregate, consumers benefit from being allowed to buy as much as they want of any good or service for which they are willing to pay at least what it costs to produce it.

Patent law, therefore, can be interpreted as an imperfect response to a Catch-22 dilemma. When patents are enforced, they may lead to high prices and inefficiency. But not having patent

protection is likely to be even more inefficient. Without the incentive patent protection gives for developing new products and technologies, R&D spending might dry up. With less inventive activity, the drug therapies would gradually stop improving.

The conflict between static efficiency (making the best use of resources with given technology) and dynamic efficiency (devoting the right amount of resources to developing new technology) can be addressed in various ways. One approach is to balance the two by having patent laws that limit the duration of patent protection: a shorter period of patent protection will reduce the incentive to develop new products and technologies, but the static efficiency losses associated with monopoly pricing also disappear when the patent expires.

A second or supplementary approach is to combine reasonably limited periods of monopoly protection with some element of price control to limit the extent to which the patentee can exercise its monopoly pricing power[6].

Since 1987, Canada has adopted the approach of combining reasonable periods of monopoly protection for medicine patent holders (both foreign and domestic) with a limited degree, of restriction on the maximum prices that can be charged in Canada.

[6] Of course, there are other approaches to deal with the inherently conflicting objectives. Prior to 1987 Canada compelled holders of patents for the production of medicines to license production of the patented product to a willing Canadian producer. Alternatively, a government can directly subsidize R&D rather than providing monopoly protection but accept that most of the benefits from this approach will flow to consumers in other jurisdictions. An additional approach for a government is to create a monopsony purchaser of patented drugs and bargain a price at which the medicine will be supplied to all consumers (public and private) in its jurisdiction.

Monopoly Protection: National and International Perspectives

Under the patent system, high prices for patented products are justified because they allow the successful developers of valuable new technology to recoup the R&D costs that had to be incurred in creating it. But technology is global. Once R&D anywhere in the world has resulted in an invention, the knowledge on which it is based can be used anywhere, not just in the country where the R&D was done. Patent legislation in individual countries generally does not discriminate between foreign and domestic inventions, and it is safe to assume that the number of patents owned by domestic inventors and firms is smaller than that owned by foreign ones in almost every country in the world. In the case of pharmaceuticals, most R&D and applications for patents come from large multinational firms whose shares are held by investors in many countries and who conduct their business through subsidiaries in many countries. Although such firms are typically classified in statistical reports as being from the country where they have their head office, the revenue they earn comes from all over the world, and the incomes they generate, for shareholders and employees, go to individuals in many countries as well.

Because the potential benefits of new technologies are shared by all countries in the world, and because the revenue from sales of patented products that are based on these technologies depends on patent laws in many countries, patent legislation has featured prominently in negotiations regarding international economic relations. In these negotiations, small countries that devote a relatively small portion of their economic resources to R&D and invention have had to consider the question why they should enforce

patent legislation that mostly enhances the revenue of firms that are foreign-owned multinationals.

Canada is one country in which this logic is relevant. Seen in isolation, strong patent laws that increase the profits of foreign multinationals don't seem to be in Canada's national interest. By itself, the Canadian economy only accounts for a small share of the global market, so reduced revenue from sales of patented product in Canada alone would not imply a large decrease in total revenue, and hence would not have a significant impact on global R&D and the flow of new products and technology. In principle, less generous patent laws in Canada might not even have a major impact on the R&D and inventive activity of *Canadian* firms. Like their multinational counterparts, they also market their patented products throughout the world, so for them too, the Canadian market will only contribute a relatively small share of their expected total earnings from a successful innovation.

When C-22 was introduced in 1987 to extend a comparable level of patent protection for medicines as existed in countries with strong pharmaceutical industries, the hope was that pharmaceutical firms would come to undertake in Canada levels of R&D comparable to that in other countries with strong patent protection. Indeed in exchange for the 1993 amendments to the Act which strengthened drug patent protection, Canada's research-based pharmaceutical companies (recently rebranded as "Innovation Medicines Canada" or "IMC") committed to double R&D output in Canada to 10% of sales[7].

[7] Pharmaceutical Manufacturers Association of Canada. Letter to the Honorable Michael Wilson, Minister of Industry, Science and technology, dated June 10 1993.

Without a major increase in domestic R&D activity, some argued at the time that Canada would be better served by having weak patent laws, or no patent protection at all. If it had followed such a strategy, Canada would have engaged in a form of "free riding". It would rely on other countries to supply most of the incentives and financing for costly R&D, while continuing to benefit from the flow of new inventions.

At first glance, a free-riding strategy may seem attractive. From a broader and more realistic perspective, however, it clearly is not viable. International negotiations regarding patent legislation (or more generally legislation on Intellectual Property which also includes copyright and trademark laws) are part of a process in which countries negotiate about mutual market access in international trade and other economic relations. In these negotiations, they try to reach mutual agreement regarding rules that all of them will abide by because doing so will benefit them all collectively. Attempts by any country to become a free rider with respect to R&D costs will be recognized and have consequences, in the form of fewer concessions in areas of particular interest to the offending country, or demands that it assume a greater share of the cost of reaching other international objectives, such as fighting climate change[8].

Consumer Protection: The Role of the PMPRB

The PMPRB was created in 1987 as part of a major overhaul of Canada's medicine patent regime, which sought to balance potentially competing policy objectives. On the one hand, as indicated above, the government strengthened patent protection for medicines in an

[8] In her review of earlier drug patent legislation, Smith (1993) refers to a 1963 report in which the Restrictive Trade Practices Commission suggested that Canada should abolish patent protection for pharmaceuticals

effort to encourage more pharmaceutical industry research and development (R&D) investment in Canada, and to make a reasonable contribution to global R&D efforts to create valuable new medicines.

At the same time, it sought to mitigate the financial impact of that change on Canadians by creating the PMPRB. The PMPRB was described as the consumer protection pillar of Bill C-22. That description has been endorsed on multiple occasions by courts, including by the Supreme Court of Canada in 2011. The stated purpose of the PMPRB was to ensure that patentees did not abuse their newly strengthened patent rights by charging consumers excessive prices during the statutory monopoly period

PMPRB: Policy Framework

The legal basis for PMPRB's regulatory role is in the 1987 Patent Act in which it is given the role of ensuring that patentees of medicines don't charge "excessive" prices. Subsection 85 (1) of the Act specifies, in general terms, the factors that the Board is supposed to take into account when deciding whether or not a price charged in Canada is excessive, including the prices of "other medicines in the same therapeutic class" in Canada, and the prices at which the medicine has been sold "in other countries", as well as changes in the Consumer Price Index over time. The Act does not, however, provide further detail and also says that the Board can consider "such other factors as may be specified in any regulations made for the purposes of this subsection" (27).

The current Patented Medicines Regulations set out what information patentees are obliged to supply to the Board, and provide the current list of "other countries" that the Board uses as the basis for international comparisons when it decides whether a price in Canada will be considered excessive. The Regulations, however, do not describe in detail how the Board carries out its functions; this information is found instead in the Board's non-binding Compendium of Policies, Guidelines and Procedures, usually referred to as the Guidelines (27). The Board itself has authority to modify the Guidelines, but is required to consult with relevant stakeholders when doing so[9].

PMPRB: Current Procedures

Under current procedures, a patentee who wants to sell an approved medicine begins by submitting a lot of technical information about the drug, including estimates of its effectiveness compared to any existing drugs that are used for patients with similar health problems, as well as the prices at which it proposes to sell different dosages of the medicine, and information about the prices at which the drug is sold in the other seven countries on the PMPRB's current list ("the PMPRB7").

Based on the clinical information, the PMPRB's Human Drug Advisory Panel then decides, first, whether the medicine should be classified as belonging to an existing therapeutic class, and second, where the medicine will be placed among the different categories the Board uses in when evaluating its effectiveness. These categories are:

[9] The Guidelines are not binding and the Board can only order price reductions following a public hearing before a Panel composed of board members.

- breakthrough medicines
- medicines that imply a "substantial improvement" in comparison with the effectiveness of existing drugs in the same therapeutic class
- medicines that imply a "moderate" improvement
- medicines that imply a "slight or no" improvement

Given the drug's classification, the Board then uses information on the prices at which the medicine is sold in the comparator countries, and the information it has on the prices of other medicines in the therapeutic class in which the medicine has been placed, to determine what it calls a Maximum Average Potential Price (MAPP) for the new drug. A given price at which the patentee has sold the new medicine, or is proposing to sell it, is then assessed by Board staff as "potentially excessive" if it is higher than the MAPP. In most cases when a proposed price is classified as potentially excessive through this procedure, the patentee will initiate a voluntary compliance undertaking usually to replace the price of the drug and pay back part of the past earnings. In the rare cases when it does not, there will be a hearing before the Board, which then has authority to decide if the price is in fact excessive and through a Board Order to force a price reduction and require the patentee to pay back all or part of any past excess earnings.

The way the Board determines the MAPP for a particular medicine depends on how it has been classified, but in all cases it normally is based on either the median value of the prices at which the medicine is sold in the PMPRB7 countries (this is usually referred to as the Median International Price Comparison, or MIPC), or on one of the prices at which other drugs in the

same therapeutic class are sold (the acronym here is TCC, for Therapeutic Class Comparison). Specifically, the rules are as follows:

- For a breakthrough medicine, MAPP < MIPC.
- For a "substantial improvement" medicine, MAPP < max [MIPC, max [TCC]].
- For a "moderate improvement" medicine, MAPP < max [(MIPC + max [TCC])/2, max [TCC].
- For a "slight or no improvement" medicine MAPP < max [TCC].

Here, for example, max [TCC] means "the maximum (highest) price in the same therapeutic class, and max [MIPC, max [TCC] means "the higher of MIPC and max [TCC]". (27, Schedule 8)

This set of rules applies in all cases when a determination is made for a newly introduced medicine, with one exception: if its application would lead to a price that is higher than the *highest* price in any of the PMPRB7 countries. (Note that this could only happen if max [TCC] is higher than MIPC.)

Patentees must continue to report the prices that they charge in later years as well, and as long as they do not increase their prices at a rate that is higher than the rate of general price inflation (as measured by the CPI), their increased prices will not be considered excessive. Once again, however, prices in subsequent years also cannot exceed the *highest* price among those charged in the PMPRB7 countries.

Critique of the Current Procedures

Since the explicit role of the PMPRB is to provide some degree of "consumer protection" against "excessive prices" charged by a monopoly provider of a patented medicine, it is not surprising that there has been criticism of the current operation of the system by those who pay for drugs (individuals and their insurers) and the producers of products (the patentees). While the PMPRB has been largely successful to date in securing voluntary compliance by the industry with its determination of maximum acceptable prices, the rising cost of new innovative treatments and the lack of transparency of actual transaction prices has given rise to calls for a modification of the regulations under which the PMPRB operates and for a "modernization" of procedures followed by the PMPRB. Before turning to a description of the proposed amendments to the regulations in the next section, we conclude this section with a brief summary of the criticisms of the current system that the proposed changes are supposed to address.

Consumers of pharmaceuticals as represented in most instances by private and public insurers face rising costs of high priced new specialty medicines. The number of drugs which cost in excess of $10,000 per year of treatment has risen sharply from 20 in 2015 to 135 in 2016 and projected to continue to increase[10]. This impact has been particularly striking in the private insurance market where the share of claims for accounted for by medicines that exceed $50,000 per year has grown to 7.4% of all claims for patented medicines. High cost specialty medicines now account for nearly one quarter of public and private insurance costs taken together.

[10] See 15: PMPRB Guidelines Modernization Paper, June 2016. Also 1, CG1: Page 3.

These trends have created greater calls for the PMPRB, as a de facto price regulator, to hold down the maximum permitted prices of these desirable but high cost innovative medicines. Consumers and payers have criticized the PMPRB as it currently operates for not taking into account the "willingness and the ability to pay" of the payers. It has been argued that this lack of "toughness" in the determination of what price is "excessive" stems from the fact that the current regulatory framework does not provide additional tools beyond price comparisons – both international and domestic – for the PMPRB to determine whether a price is "excessive".

Some analysts have argued that in addition to national and international price comparisons, the PMPRB should take into account whether the price for a medicine is commensurate with the benefits it provides to patients in the context of the Canadian health care system. However, others have questioned the appropriateness of using cost utility analysis (a form of health technology analysis, or HTA) strictly for the purpose of price regulation. Analysts also have argued that the impact of an "excessive" price is a function of volume as well, and that the PMPRB should consider the size of the domestic market in determining excessive prices. In addition to determining MAPP at time of introduction, many argued that the PMPRB should track the evolution of the price of a medicine over time to align and correct MAPP downwards if appropriate to the evolution of the market size for the medicine. This downward price trajectory over time is commonly observed in other countries with comparable health care systems.

To address the issues of willingness and ability to pay, the government proposed that new economics-based regulatory factors be considered by the PMPRB. These new factors are described in Chapter III below. The impact on prices and revenues – net costs and benefits – is analyzed in Chapters IV and V.

Not only has the PMPRB not taken demand side factors into account, in the critics' view, but it has also been argued by some that the way the PMPRB carries out international price comparisons leads to an upwards bias in determining the Maximum Average Potential price (MAPP). In particular, they have claimed that the set of seven countries used to track international comparison prices in order to determine the MIPC is inappropriately narrow and unrepresentative of countries like Canada. An expansion of the list of comparator countries would produce a MIPC that would be more representative of the median OECD price, and hence more appropriate for PMPRB to use.

The final major critique of current regulations and practices relates to transparency of the prices which are subject to PMPRB scrutiny. In an era when public list prices may not actually reflect what private and public insurers are actually paying for patented medicines, it is highly problematic that the PMPRB makes its assessment almost entirely on the basis of domestic and

international publicly available ex-factory prices. Because this leads to a high effective maximum regulated price, critics have argued that the consumer is not adequately protected against excessive prices[11].

The regulatory changes proposed by the government to address the price transparency issue and all the other issues set out in this critique section are described in Chapter III and the empirical impact of these changes analyzed in chapter IV and V.

[11] The government stated that some very high price, high R&D countries (such as the U.S.) do not have policies well aligned with the consumer protection mandate of the PMPRB and hence, should not be included in the list of comparator countries. It is also argued that unlike Canada these countries benefit from very high R&D spending by pharmaceutical companies. To some analysts, including ourselves, this second argument does not seem to be a totally compelling reason for the exclusion. However, since it is the median – not the average – international price that matters, excluding the US & Switzerland from broadened comparator a base of 14 countries should not matter that much empirically, except perhaps in cases where the only external price that is available is from the U.S..

CHAPTER III

The Proposed Amendments to the Regulations

In the RIAS submission, the proposed regulatory reforms are described as consisting of five elements:

- introducing three new price-regulatory factors that the Board can consider;
- updating the PMPRB7 country list;
- reducing patentee reporting requirements for veterinary, over-the-counter and generic medicines;
- adding certain reporting requirements relating to the new factors; and,
- requiring patentees to inform the Board with respect to third-party discounts that currently are confidential.

Items 3 and 4 in this list are relatively straightforward and non-controversial, and did not have a major impact in the Cost-Benefit Analysis. Hence we focus on items 1, the "new factors", 2, the updating of the schedule of countries, and 5, the confidential discounts.

The New Factors

In the RIAS, three new "economics-based regulatory factors" are listed and described under the rubrics "pharmacoeconomic value", "size of market", and GDP. The justification for

introducing these factors is only briefly discussed in that document; a somewhat more extensive discussion is in Health Canada's May 2017 consultation paper (13).

Pharmacoeconomic Value

As the various discussion papers have noted, pharmacoeconmic evaluations in which attempts are made to quantify the expected health benefits of medicines are playing an increasingly important role in the markets for pharmaceuticals across the world. Typically, the quantification takes the form of estimating the increase in years of quality-adjusted life expectancy (QALYs) that can be expected from a new medicine, in comparison with relevant alternatives. In cost-utility analysis (CUA), the expected increase in QALYs is then compared with the additional cost that using the new medicine entails, and a number referred to as an Incremental Cost-Effectiveness Ratio (ICER) is calculated by dividing the expected additional QALYs by the additional cost. Accordingly, the ICER can then be interpreted as a measure of the cost of generating an additional quality-adjusted life year by use of this medicine, and this number can then be compared with ICERs that have been computed for other medicines or health system interventions that represent alternative ways of creating additional QALYs (that is, alternative ways to promote population health).

The logic underlying CUA, or indeed any form of cost-effectiveness analysis, is that if the decision-maker (usually a payer) has a limited budget to spend, it should be spent on those medicines or interventions with the lowest costs per unit of benefit (in the healthcare case, the lowest ICERs). This, it is hoped, will imply that a fixed budget gives the largest possible benefit

in the form of better population health. Application of the model in practice tends to be based on establishing certain critical values of the maximum cost per QALY that the decision-makers would be prepared to pay for a new medicine or technology, given the alternative ways that their budgets could be spent.

In Canada, there are already two major agencies, CADTH and INESSS that routinely engage in estimating the ICERs for new medicines or other health system intervention and have considerable expertise with CUA methodology. Accordingly, PMPRB would be able to incorporate CUA in the regulatory process without having to create its own capacity to do the required analysis. Indeed, it is likely that CUA already is playing a major role in the way medicine prices are established in Canada currently. Although we do not know the exact nature of the way negotiations about drug prices currently take place when the government drug plans that belong to pCPA negotiate with pharmaceutical suppliers, it seems likely that the information about the ICERs that is available from CADTH and INESSS play a considerable role in making the suppliers offer discounts that are deep enough to make the net prices lower than what corresponds to the maximum costs per QALY that government (and private) insurance plans are prepared to pay.

As discussed in Chapter II, the underlying logic of the international patent system is that the potential monopoly profits that patentees can earn serve as an incentive for them to engage in the R&D that is necessary to develop new medicines and other products. Given this, it makes sense to allow them to charge prices that reflect the maximum amount that payers, as representatives of society, are willing to pay. In deciding whether they are willing to pay a

patentee's proposed price for a given drug, payers will weigh that price against the expected health benefits that the drug promises to yield. But that is exactly what CUA tries to do, so for payers, CUA can indeed by a useful tool.

A regulatory agency such as the PMPRB in the Canadian system, however, does not play the role of a payer. In our system comprised of a multiplicity of public and private insurers, its mandate is to protect Canadians against "excessive" drug prices, not to negotiate with suppliers about prices and other conditions that will govern the future utilization of a given drug. Payers can do the latter. For example, in several European countries, suppliers of particular drugs have agreed that the net prices they will be paid will partly depend on the extent to which the drugs actually help improve patients' symptoms and health outcomes. Payers, therefore, can use CUA in a flexible way, as one of several tools that guide their decisions. For a regulatory agency that is supposed to operate under explicit and transparent rules, this may be more difficult.

Moreover, while the general methodology of CUA is widely accepted, some aspects of it remain controversial, and there is still a great deal of variation in the way it is used in practice.[12] For all these reasons, therefore, careful consideration should be given to the issue of precisely how CUA or other forms of HTA should be introduced into the price regulation process in Canada.

Although we think that tests based on international or therapeutic class comparisons are likely in most cases in practice to be constraining element in the PMPRB's determination of the

[12] For example, most economists would argue that the natural way to conduct CUA is by applying a societal perspective: that is, the cost concept that should be used to estimate an ICER should include costs borne by anyone, not just by the agency that pays for the drug. According to what we have been told, however, in the CUAs conducted by CADTH, the only costs that are included are those borne by the paying agency.

maximum non-excessive price, we believe that pharmacoeconomic evaluation should be one of the factors that the PMPRB should take into account.

Market Size and GDP

While HTA and CUA are based on methods that stem directly from microeconomic theory, the economic logic with respect to the other proposed new factors, market size and GDP (in the aggregate or per capita), is somewhat less clear. The discussion in the background papers (13, pp 10-11) appears to make the case that if the predicted sales of a new medicine are large at the time it is introduced, the maximum regulated price should be lower than it otherwise would be. Similarly, if subsequent sales exceed expectations, for example, because a medicine becomes used for other patient categories than originally foreseen, the regulated price should be lowered.

Regulations or negotiations in the pharmaceutical sector in other countries have taken considerations of this kind into account in the past, and systematic methods for quantifying them have appeared in the literature (see the Hollis and ICER models, in 5). One justification that is sometimes heard is that when expected sales are large, or actual sales end up larger than expected, patentees may be able to charge a lower price and still "recoup [their] initial

investment" (13, p 10). However, the logic of the patent system cannot be that prices for patented products should be just high enough to pay for the R&D that went into the development of those that were successful. Whether R&D with respect to a particular medicine will be successful or not cannot be known in advance. In many cases, it is not, so the R&D expenditures for that drug will never be recouped. To compensate for the risk that this may happen, it is necessary that the profits that patentees can expect to earn on successful medicines must be large enough to enable them to cover aggregate R&D expenditures on both successful and unsuccessful ones.

Another argument for letting market size influence the regulated price is that payer budgets can be inflexible, so that larger-than-expected spending on a successful medicine may be result in rationing or damaging cutbacks on other medicines or expenditure categories, especially in the short run. To allow for this, pricing agreements that involve a certain amount of risk-sharing between payers and sellers certainly may make sense; such risk-sharing can indeed take the form of a price reduction if the volume of sales is higher than anticipated. Note, however, that this argument principally applies if total expenditures over time end up being higher than anticipated, and should carry less weight for regulating the price of medicines at the time when they are first introduced.

Finally, the suggestion that price regulation should also take into account a country's GDP (or GDP per capita) partly reflects the notion that the global burden of sharing the cost of pharmaceutical R&D should be distributed in a way that depends on countries' relative ability to pay. In countries where medicine pricing reflects pharmacoeconomic evaluations, such burden-

sharing already is likely to take place to some extent: the critical ICER values of costs per incremental QALY will tend to be higher in wealthy countries with large per capita healthcare budgets than in poor countries with lower budgets, i.e. GDP and high ICERs partially get at the ability-to-pay factors. This implies that prices for similar drugs will tend to be higher in wealthy countries.

Updating the PMPRB7 Schedule

In Health Canada's 2017 consultation paper (13, p 12) the case for updating the schedule is reflecting a desire to base the tests in which medicine prices in Canada are compared with those elsewhere on data from "countries that are more aligned with Canada economically and from a consumer protection standpoint". In practice, this translated into a proposal to delete the two countries with the highest GDP per capita from the list (the US and Switzerland, who also are the countries that often are shown with the highest medicine prices in international comparisons; (14, p 16)), and adding 7 new countries, including Australia, Japan, the Netherlands, South Korea, Norway, Belgium and Spain.

Deletion of the two countries with the highest per capita income from the PMPRB7 list can, in part, be seen as reflecting the same idea as that referred to above, namely that in its medicine pricing policy Canada should be willing to carry a share of the burden of pharmaceutical R&D that is similar to that of countries with a comparable ability to pay, as measured by per capita income for example. The new list does include Norway, a country with very high per capita income, but with medicine prices that by one measure tend to be lower than

those in any of the countries on the original PMPRB7 schedule. The PMPRB modernization paper (14) does not elaborate on what is meant by the phrase "more aligned with Canada .... from a consumer protection standpoint", but it is noteworthy that all the new countries on the list (now often referred to as the PMPRB12) are countries with universal health insurance, in most cases provided through government plans.

In its discussion of the rationale for updating the schedule of countries, Health Canada also notes that when the 1987 Patent Act was passed and the Board was created, the pharmaceutical industry had made a commitment to increasing its R&D spending *in Canada* to 10% of its Canadian revenues. Indeed, under the 1987 Act, the Board has both a regulatory and a reporting mandate, where the latter includes annual reporting "on pharmaceutical trends and on the research and development (R&D) spending by patentees". Based on its definitions of R&D spending, recent PMPRB data show that this commitment has not been met (13, p 12 cites the PMPRB Annual Report of 2015 as showing a percentage of only 4.4%, as opposed to 22.8% in the PMPRB7 countries). The industry, however, claims that the definition of R&D spending that PMPRB uses is outdated, and that by more reasonable measures the commitment has been met.

Reporting Confidential Discounts

As discussed earlier, the increasing use of confidential discounts has over time, made publicly available ex-factory prices less and less accurate as measures of the average net revenue per unit that pharmaceutical companies earn from the drugs they sell. This is relevant both with respect to the usefulness of international data on list prices as a basis for regulation in Canada,

and with respect to the question whether the PMPRB should continue to assess regulatory compliance by looking just at data on patentees' publically available reported net ex-factory prices, or whether they should attempt to take certain confidential discounts into account when doing so[13]. PMPRB and HC (14, p 16 and 13, p 9) both cite the "inherent unreliability of international public list prices" as a major reason for giving the PMPRB additional regulatory tools. PMPRB (14, p 18) also observes that the desire for better price transparency in the worldwide pharmaceutical industry "will undoubtedly require international cooperation". In principle, Canadian regulation could attempt to obtain more accurate information about confidential discounts that pharmaceutical companies grant payers in other countries as well, but enforcing such a rule would obviously be difficult. However, information about confidential discounts that are granted to buyers in Canada would be easier to verify, and could be used to create a regulatory process that potentially would be very different from the present one.

The PMPRB paper (14, p 17) emphasizes the idea that better information about actual net prices (i.e., after confidential discounts) could provide a better basis for that part of the process that relies on comparing the proposed price of a new medicine with the domestic prices of other medicines in the same therapeutic class (TCC). Often these are new drugs in the "slight or no improvement" category, of the type that often are referred to as "me-too" drugs, and the PMPRB paper (14, p 17) notes that the current Canadian approach to regulating such medicines is out of step with that in other countries. However, a potentially more important possibility is that the information about confidential discounts would be used to calculate some kind of further adjusted average transaction price that is different from the publicly available ex-factory price,

[13] The current regs do allow for the PMPRB to look at average transaction prices which are net of certain rebates and discounts; the proposed new regs expand the kinds of rebates and discounts that must be reported by the patentee.

and that this new adjusted price would be *used in assessing the patentee's compliance* with the regulated price. The HC consultation paper (13, p 15) explicitly states that this is the intention. Although the logic of the new reporting requirements seems reasonably simple, it may be somewhat complicated in practice. Assuming that the Board still has to determine a maximum ex-factory price similar to the current MAPP, it would also have to define a second, lower, maximum that the adjusted price, net of discounts, could not exceed. Information supplied by patentees' on third-party discounts and other rebates would then be used to determine whether they had complied with this lower limit. In order to exercise effective price discrimination, the pharmaceutical companies do not want to publicly disclose information about the discounts they grant individual payers. Hence, the proposal is that the information would remain confidential, as is all confidential information currently submitted to the PMPRB per 5.87-88 of the Act. That is, unless the information has been disclosed at a public hearing (Sn.83), it would not be available to the public, other payers, or foreign regulatory agencies.

Guideline Revisions and the CBA

The cost-benefit analysis (CBA) of the impact of the proposed regulatory changes that we were asked to assess, has been carried out by Health Canada, in collaboration with PMPRB staff. A CBA must accompany any proposal for regulatory reform, and even though the PMPRB operates "at arm's length" from the government, ultimate responsibility for federal regulations related to the prices of patented medicines rests with the Minister of Health, so Health Canada was tasked with performing the CBA.

As observed above, the current instrument that sets out the regulations is very brief. The document that describes how the PMPRB staff review prices in detail is found in the Compendium of Policies, Guidelines and Procedures (27). The Board itself can modify the Guidelines document, although the regulation specifies that in doing so, it must consult with relevant stakeholders.

Technically, the elements of the proposed changes described in the previous section refer to changes in the language of the Regulations. However, the effect that they ultimately will have on the market for pharmaceuticals will depend heavily on the detailed way that the Board will use the new tools that it will have as a result of these changes. Consequently, a meaningful CBA of the changes to the regulations can only be undertaken on the basis of fairly detailed specific assumptions about how the Board will modify and apply its Guidelines following the proposed changes in the Regulations language. In these circumstances, it clearly made sense for Health Canada's CBA to be conducted in close collaboration with Board staff. It also makes sense for the Board to consult "with the relevant stakeholders" in advance, so that the implementation of the revised regulatory regime can happen relatively quickly after the Regulations have been changed.

The CBA accompanying the RIAS submission was done by Health Canada using projections, data and input from PMPRB staff. Stakeholders were invited to submit comments on a document entitled PMPRB Guidelines Scoping Paper (12) in which many of the planned changes in the Guidelines were described. However, the Scoping paper only described these changes in very general terms. Moreover, as we discuss in the next Chapter, the CBA did not

provide full detail on the planned changes, and finally, later information has made it clear that the final Guidelines may well be quite different from those that were the basis of the CBA. Much of stakeholders' concerns could have been avoided if a clear description of the assumptions made by the CBA had been provided from the outset, even if such a description is not provided for in the TBS guidelines. Going forward, an open and transparent consultation process in this respect could be very helpful in reducing stakeholder uncertainty.

The Scoping Paper

The Scoping Paper (12) begins by describing the way new drugs will be placed in two new categories, High Priority Drugs (Category 1) and Medium and Low Priority Drugs (Category 2). This classification is somewhat different from the one that is currently being used, in part because it is based not only on the presence or absence of therapeutic alternatives, but also on factors such as expected market size and annual cost per patient.

For both categories, the initial assessment of a proposed price for a new drug would be an international price comparison (but based on data from the new list of comparator countries). If a new drug is then classified in Category 1, its price would also be tested against several of the "new factors" (that is, whether it is low enough so that treatment with the drug meets given thresholds for the cost per QALY, and whether it is low enough so that its total impact on payers' drug budgets falls below certain market-size thresholds. In addition, an adjusted price net of planned confidential rebates would be tested against an index of net Canadian prices of other drugs in the same therapeutic class; this test would draw on the new reporting requirements

that would be part of the new Regulations. A noteworthy feature of the scoping document is that the threshold value for the adjusted price would be confidential; that is, only the maximum list price resulting from the initial international price comparison would be publicly known (12, p 7). For drugs placed in Category 2, a "revised therapeutic class comparison test" would be used (p 7); under it, the proposed price of a new drug would no longer be compared with the highest one in the same therapeutic class (as it would be under the current system), but would instead require "each successive entrant to reduce its price relative to the price of the drug that preceded it" (12, p 7)[14]. Finally, the Scoping Paper introduces the concept of "re-benching"; it refers to the possibility of revising the original ceiling price on the basis of new information such as a change in market size if a drug becomes used by patient categories other than those originally foreseen, etc.

The Scoping paper gave a clearer indication than the earlier consultation documents regarding the way the Board might use the new tools that the revised Regulations would put at its disposal. However, the question how significant the ultimate impact on the pharmaceutical industry would be remained highly dependent on certain critical Board decisions and parameter choices that had not yet been discussed in detail. These included issues with respect to the exact methodology it would rely on for establishing whether a new drug would meet the threshold value in the pharmacoeconomic evaluations in Category 1, as well as what the critical threshold values would be for different drugs, and what methods would be used to account for the market size and GDP factors. For Category 2 drugs, there was some uncertainty with respect to the nature of the revised therapeutic class comparison test, and how the principle of rebenching of

[14] More recently, PMPRB has indicated that the discount information would not be used in this manner. Instead, the discount/rebate information would principally allow patentees to demonstrate compliance with non-excessive price ceilings - while also maintaining non-transparent market prices in Canada (15, 28).

the ceiling price in later years would be implemented. Some of the uncertainty, but not all of it, was resolved with the publication of the CBA that was done at the time of the CG1 publication. We discuss it in detail in the next Chapter.

CHAPTER IV

Assessment of Health Canada's Cost-Benefit Analysis

Introduction

The cost-benefit analysis paper prepared by the Strategic Policy Branch of Health Canada (3) constituted a reasonably refined effort to make a quantitative estimate of what impact the proposed regulatory changes might have on prices of patented medicines and the revenues of the pharmaceutical industry in Canada. A summary of the cost-benefit analysis was included as part of Health Canada's CG1 submission, but the submission states that what is described as the "complete" version is available on request. We will henceforth refer to this version (3), which is a 38-page document as "the CBA". It draws heavily on the extensive expertise and public and confidential data on the industry, in Canada and internationally, that the staff of the Board possesses. However, most of the quantitative estimates in the CBA were provided without much explanation the methodology used. In order to make our assessment we have had to rely on a number of working documents, including decks (4 and 5) and computer files (6 and 7), which were not originally made publicly available.

Based on the additional detailed material that has been provided to us, we judge that the empirical analysis of the baseline future industry revenues and the impact of proposed regulatory changes on those revenues has been carefully done, and was done based on judicious use of recent data and on not unreasonable assumptions about the application of the new operating Guidelines that will be formulated and published after the final regulation changes are gazetted.

The Health Canada paper uses the classic cost-benefit analysis approach favoured by the Treasury Board, in which the effects of a proposed action are evaluated by constructing alternative scenarios in which the variables that are of interest are predicted with and without the actions that are contemplated. In this case, the relevant variables are prices and expenditures on various categories of medicines and (to a minor extent) on the administrative costs incurred in the regulatory process, while the proposed actions are the changes to the regulatory process that were described in the previous Chapter. The predicted values of the relevant variables are then aggregated into measures of total benefits and costs, expressed as present discounted values, and combined into a measure of the estimated net benefit to Canada over the period covered in the analysis, which is the 10-year interval 2019-2028.

The forecasts of expenditure on medicines in different categories, and of the estimated impacts associated with the different posited regulatory regimes, thus are the essential elements of the cost-benefit analysis. Expenditure forecasts are inherently uncertain, especially when they depend on factors such as the success or failure of the R&D that aims to produce new medicines, meaning that the forecasts themselves, particularly those that relate to years far into the future, have large margins of error. Moreover, in carrying out the CBA, HC had to make specific assumptions about how the new regulations will be interpreted and how the PMPRB Guidelines will be adapted. This adds a further large dimension of uncertainty to the estimated impact of the proposed regulatory changes. The authors of the CBA implicitly recognized these sources of uncertainty and provided calculations which suggest that the range of plausible future values of the variables of interest can be very wide indeed (see3, pp 31-34).

The CBA Document: Some Initial Comments

The quantitative estimates of the impact of the proposed reforms appear to have been very competently done, on the basis of the best available data and using a combination of relatively sophisticated methodology and informed professional judgment. That said, however, our favourable view of the quality of the work that went into the CBA is to a large extent based on meetings and informal conversations with those who did the work, and supplementary material that they have given us.

As already noted above, among the parameters values that had to be assumed were several that would depend on decisions with respect to the way the Guidelines would be changed. From the additional material we were given by HC and PMPRB, we were able to infer the intended Guidelines changes that were used in the CBA. However, it has subsequently become clear to us that many of these Guidelines provisions remain subject to change. In particular the document released in June 2018 (8) suggests a set of Guidelines changes that differ substantially from those that were used as the basis of the CBA.

For a reader who is trying to assess whether the forecasts and estimated impacts are reasonable, therefore, the original CBA document is of little help; if one wants a better informed public debate on the issue, a version with fuller information about them certainly would be a welcome addition. By the same token if there is to be a meaningful debate about the way the Guidelines should be changed, new estimates should be provided by the PMPRB to show how

different Guideline provisions would affect the estimated impact of the new regulations. We will generally sidestep this issue in the rest of this Chapter, but return to it in Chapter VI.

We would also like to comment on an aspect of the CBA that may be puzzling to economists: that not much is said about the impact of the proposals on predicted drug utilization. While there is a great deal of discussion of the effects that the proposed changes are likely to have on drug *prices*, little or no attention is paid to the question how these price changes are likely to affect the quantities that are utilized in the different categories of drugs. Essentially, the approach that is used assumes that the effects on quantities utilized are going to be negligible, an assumption that economists generally tend to question.

In the context of pharmaceutical markets, however, we think the assumption of negligible quantity changes in response to changes in prices, is appropriate. Even though a small portion of total drug costs are paid for out of patients' own pockets, most is paid for by third-party insurers who have no influence on what drugs are prescribed and only limited influence on utilization. The result is a market in which quantities demanded are likely to be almost totally insensitive to the prices that sellers charge because, "those who choose do not pay, and those who pay do not choose".

If the price is set too high, third-party payers may refuse to reimburse patients for the drug, causing reduced sales. But for the most important indicated use of a drug, this is not the usual outcome since it is not in the seller's interest to set a price high enough so that this

happens. On balance, therefore, we don't think the CBA should be criticized for making the assumption that the reforms are unlikely to have a major impact on drug utilization.

Looking at the supply side, it is true that a very stringent price ceiling in Canada may cause some patent holders to delay the timing of introduction of some valuable drugs in this country. The industry has raised this concern. This may well be a legitimate issue that Health Canada needs to consider but it relates more to the *timing* of introduction of particular drugs, and is not likely to be a major consideration when one is making empirically based forecasts of the growth of industry revenues in aggregate[15].

Predicting The Impacts of the Reforms: The Baseline

The first step in the estimation of the impacts of the various reform elements was creation of a baseline scenario to predict what various kinds of drug expenditure would be if there was no change in regulations. No document that gives full details of the way the baseline was constructed is publicly available, but we have received a great deal of information about the methodology in meetings and via computer files.

Critically, consistent with the Scoping Paper (12), the baseline forecast distinguishes between "existing" drugs (that is, those that had already been introduced in pre-scenario years), and "new" drugs[16]. For "existing" drugs, predictions of sales in the scenario years (2019 to

[15] Delay in timing of introduction is of course a concert to the patients who may benefit from the drug..

[16] Both the CBA and the PDCI paper assume that the proposed regulations would apply to "new" drugs only. "Existing" drugs, i.e. those introduced before 2019 would be largely unaffected. Moreover, it was assumed that the pharmacoeconomic factor would not affect the classification into category I or I.

2028) were done on the basis of time trends estimated from past sales. Sales of individual drugs were assumed to continue growing at the observed trend rates until they lose market exclusivity, after which time they were forecast to decline in accordance with one of two "erosion curves" estimated from historical data. Separate forecasts were done for some 200 different existing drugs. For each one, additional information about its characteristics was used to establish whether it should be classified in Category 1 (High-Priority Drugs) or Category 2 (Medium and Low Priority). The classification was based on criteria such as whether a drug was "first in class", had few therapeutic alternatives, was indicated for conditions that have a high prevalence in Canada, or for a condition that appears on a list of Rare Diseases, was a high-cost drug in terms of the annual cost of treatment of a patient taking it, and so on (12, p 6).

Similarly, arrival of "new" drugs in different categories was predicted on the basis of data on the rate of introduction of new drugs in the recent past (2009-14)[17]. Sales of new drugs in subsequent years also were predicted by looking at how sales of newly introduced drugs had performed over the 2010-2015 period. The share of sales of "new" drugs that would fall in Categories 1 and 2 going forward was assumed to be the same as was observed for drugs introduced during the sample period (5).

The individual forecasts for sales of existing drugs and those for sales of new drugs were finally aggregated into just four sequences for the 10 scenario years 2019 to 2028: Sales by year for Existing Drugs in Category 1 (High Priority Drugs) and Category 2 (Medium and Low Priority), and for New Drugs in the same categories. In all cases, the estimated impacts of the different elements of the proposed regulations that are used in the CBA were based on

[17] Forecasts may be very sensitive to the precise time period chosen as the basis for it.

forecasting how these four sequences would change in response to the proposed regulatory process (5 and 7).

As should be clear from the above, the methodology that was used to construct the baseline was highly sophisticated, and made good use of the available data. Although some might argue that some alternative assumptions and procedures could have been used if the objective was to provide the best possible forecasts of future drug expenditure - that was not the purpose. The goal instead was to use simple procedures to produce a plausible baseline to be used in the subsequent impact analysis. In our opinion, the analysis clearly provides a reasonable baseline forecast for sales.

While we think the baseline estimate (based on the assumption that the new regulations would apply to new drugs only) is quite reasonable, we also believe it would have been useful if the CBA document had provided a more detail about how it was constructed, perhaps in an Appendix. We also note that even though the CBA does have a table that summarizes the baseline (3, Table 2, p 15), the "medicine categories" that are given in that table are different from those that were subsequently used in the analysis of the impact of the different new regulatory elements. If a revised version of the CBA document were to be produced, it would be helpful to the reader to be shown the four basic forecasts sequences that were subsequently modified in order to produce the estimated impacts shown in later tables.

In the next three sections, we turn to the methods the CBA used in predicting the impacts of the three fundamental elements of the proposed reforms: the New Regulatory Factors, the new Schedule of comparator countries, and the new Reporting Requirements.

Proposed New Regulatory Factors

The estimated impacts of the New Factors in future years shown in Table 3, p 19 in the CBA are easy to calculate from the four fundamental baseline series: it simply is 40% of the entries in the New Category 1 drug expenditure series. That is, if new price ceilings were imposed that reflected those factors, predicted expenditures on new drugs classified in the High Priority category would be 40% lower than they would be under the current regulatory regime.

The 40% reduction is not an assumption; documents (5, 7) make clear that it is based on a careful analysis of PMPRB data for drugs that were launched in the period 2010-15, and on data from a sample of 46 drugs for which a cost-utility analysis had been carried out by CADTH so that an estimated cost per incremental quality-adjusted life year ($/QALY) was available. In this analysis, the hypothetical question that was asked was: if at the time a drug was introduced, regulations had been in place that defined a maximum price that could be charged for the drug, either on the basis of its estimated cost in terms of $/QALY, or in terms of its projected total expenditures or its estimated development cost in relation to Canada's GDP, how much lower would the price of that drug have had to be than the average transaction price that the seller was allowed to charge under current regulation?[18] The tests were applied to each drug individually, and in combination. By itself, the $/QALY thresholds that were used would have led to a 33% price reduction on average, while the specific tests reflecting market size and GDP factors by itself would have led to a 29% reduction. The 40% figure results when the two tests are applied together, so that the ceiling price of each drug is calculated by whichever of the two tests yields

[18] Our understanding is that this was the average transaction price under the existing definition of the ATP, i.e. rebates not included. See 5, July 12 – Summary of the Methodology.

the lower value but in all cases the calculated percentage reduction is constrained to a maximum of 50%.

Beyond a general discussion of what factors could be taken into account, the CBA document provides no detail with respect to how the analysis that yielded this 40% parameter estimate, was carried out, or what assumptions were made in it. In material that has been made available to us (5, 7), there is information about key parameters such as the threshold $/QALY figures that were assumed for different categories of high-priority medicines (different ones were used for drugs to treat rare diseases, or conditions with high prevalence, and so on). It also gives the different formulae that were used to set price ceilings for new drugs on the basis of predicted total sales, Canada's GDP relative to other countries, or the growth rate of GDP. All the parameter values or formulae are reasonable in the sense that they come from academic studies or suggestions in the literature. Nevertheless, the choice of particular values is obviously controversial, as different parameters or thresholds could have led to very different estimates of the impact on the maximum allowable price[19]. It seems to us that assumptions made about implementation should accompany the CBA, perhaps in an Appendix[20].

Proposed Change in the Schedule

Whereas the New Factors only were intended to affect new drugs that have been classified in Category 1, the proposed change in the schedule of comparator countries will

[19] In the July 12 methodology paper (5, p. 16) PMPRB notes that by applying pharmacoeconomic analysis only, prices would be reduced on average by 33% for the 46 high priority drugs in their data set using specific cost/QALY thresholds. The EY analysis (26) indicates that the impact could be greater (26, July 5, pg. 9), as much as 40-90% for some particular drugs in the data set.

[20] We understand that according to TBS guidelines cost-benefit analysis of regulatory changes is supposed to be done on a stand-alone basis. In this case meaningful analysis can only be done on the basis of explicit assumptions about the guidelines.

potentially affect all drugs in the long run, since an international price comparison test will be conducted whenever any new drug is introduced.

Based on the supplementary information we have received, we have learned that for Category 1 drugs, the percentage reduction that would be required to align their prices with the median of the PMPRB12 schedule (as opposed to the current PMPRB7) was calculated comparing the observed average transaction prices (ATPs) for a sample of high-priority drugs in 2015 with data on the median list prices of the same drugs in the PMPRB12 schedule (available via the MIDAS database). The weighted average of the reductions in the observed Canadian ATPs that would have been required to reach the PMPRB12 median was estimated at 4.5%. Note that this percentage is smaller than if the comparison had been between Canadian *list* prices and the median prices in PMPRB12; the latter are based on list prices[21]. In part it is this factor that accounts for the large difference in the estimated impact of the schedule change between the CBA and the IMC Re-analysis that we discuss in Chapter 5.

For Category 2 drugs, the current approach to setting the ceiling on its introductory price could depend either on the *highest* price among the PMPRB7, or on the *highest* price in Canada on drugs in the same therapeutic class (or on both). Although the CBA document does not say so explicitly, we have learned that under the changes it envisaged, the ceilings may be calculated based on the *median* international price, now calculated from data from the PMPRB12, and on the *average* price of drugs in the same therapeutic class[22]. To reflect the effect of these changes, the investigators identified a sample of drugs in Category 2 that had been introduced in the 2010

[21] See 10, figure 15 on p. 35.
[22] Note that in the CBA analysis this impact is attributed to the change in reporting requirements, not to a change in the schedule.

to 2015 interval, and asked the hypothetical question how much lower their introductory prices would have had to be under the new rules. For these drugs, however, there was no attempt at using new data for the prices that had been charged for those drugs in all the countries in PMPRB12; instead, it was simply assumed that the schedule change would have implied a reduction in the median price by 15% across the board.

Based on these data and assumptions, it was found that the combination of the move to a strict median price comparison (and the assumed 15% reduction in the median price) would have led to introductory list prices that would have been 3.49% lower than those actually observed. In part, the relatively small magnitude of this effect is attributable to the fact that for many drugs in Category 2, the price ceiling is determined by the comparison with the [average] prices of other drugs in the same therapeutic class (TCC), not by the international price comparison.

These estimated effects, for both categories of drugs, are reasonable ones. Again, they are based on actually observed data and particular but plausible assumptions about the application of future Guidelines. However, we are not in a position to judge the "reasonableness" of these assumptions which imply a prediction of future Board decisions.

Each of the numbers in Table 4 where the "schedule effects" are estimated (p 22 in the CBA), is the sum of two components that are intended to measure the estimated impacts of the new schedule on drugs in Category 1 and 2. The component corresponding to Category 2 is simply the total predicted baseline spending on medium and low priority drugs, multiplied by the 3.49% described above, times a coefficient that is intended to reflect that this impact will only

occur gradually since the test only affects "new" drugs.[23] In ancillary material we have seen, this process is referred to as a "phased-in" effect.

The component that refers to high-priority drugs, in contrast, is simply 4.5% of the total predicted spending on high-priority (Category 1) drugs, new and old. (That is, there is no "phasing-in" of this effect.) The fact that it is shown as affecting not only spending on *new* Category 1 drugs is noteworthy. This approach is not consistent with the principle that the new regulations should not affect "existing" drugs, drugs that were originally introduced while the old rules applied. Although the CBA document does not say so, it appears that this calculation reflects an application of the "re-benching" principle, the principle that certain changes that affect the market for a particular drug may lead to a revision of the ceiling price that was originally foreseen [24].

Proposed Changes in Reporting Requirements

Table 5, finally, has a heading that should have been different if it was to represent the predicted effect of the new reporting requirement, but also the fact that the information that will be reported will be used in a test that is different from what applies at present. Specifically, while the price ceiling defined by the domestic price comparison (TCC) currently is based on the *highest* price in the therapeutic class as analyzed, the proposed new test would be based on the *average* price. That is, the test would be more stringent both because it will be based on the

[23] Specifically, the coefficient in year t is 0.0625*(t-2018), meaning that it was .0625 in 2019 and increased by a further .0625 in each subsequent year. The parameter .0625 is chosen because data suggest that on average, 6.25% of the aggregate spending on drugs in a given year is attributable to "new" drugs that have been on the market for no more than one year.

[24] In one of the computer files that was provided to us, the term 'rebenching" is indeed used to refer to this calculation.

average, *and* because the reported domestic prices will be lower than at present, since they may reflect third-party discounts that currently are not known to PMPRB[25].

Using the same sample of Category 2 drugs as referred to in the previous section, and assuming that the reporting requirements would have lowered the prices used in the TCC by 10%, the estimate was that the introductory prices of the new drugs in the sample would have been 4.53% lower than the observed values. The future savings that were predicted as a result of this effect were then estimated by the same phasing-in procedure as described in the previous section, to reflect that they would only occur gradually as the introductory prices of a growing share of the drugs would have had their ceiling prices established under the new rules.

Again, given the data, the procedures used to estimate these savings are not unreasonable. However, the approach sidesteps an important question: will the confidential discounts that the patentees will be required to report be deducted from the average transaction prices (ATPs) that the PMPRB calculates to determine whether they are complying with the price ceilings it has specified? If the answer is yes, as we believe to be the intention, then the estimated expenditure reductions from the application of the new regulations element may be overstated. While the new reporting requirements will, other things equal, lower the permitted price ceilings, they may also make it easier for patentees to demonstrate compliance, something that will tend to reduce the savings that will ultimately result. Thus the impact on actual prices and industry revenues is likely to be smaller than the lower price ceilings would suggest.

[25] Note, however, that the modernization deck (15) and the second Steering Committee deck (28) suggest moving away from using discount information in this way.

Calculating the Net Benefit to Canada

The preceding sections discuss the way the CBA document tries to quantify the impact that the proposed changes to the Regulations will have on various parties, *when combined with the assumed set of changes to the Guidelines that are the basis for the main estimates*. The next step in the analysis then consists in aggregating these impacts into a single measure of the net benefit to Canada. Like the component effects discussed above, the impacts are first estimated for each year over the forecast period 2019 to 2028, and then expressed as a discounted net present value. Two aspects of the way this is done in the document are noteworthy.

First, in valuing effects that occur in future years, the CBA uses a discount rate of 7%, the rate recommended by the Treasury Board. In comparison with the discount rates that typically is used in cost-benefit analysis or cost-effectiveness, this rate appears very high. For example, the "reference case rate" that CADTH uses is 1.5% (5 p 5). The CADTH rate is low in part because it is used to discount benefit and cost measures that are expressed in constant dollars, that is, have been corrected for general price inflation; the dollar values in the Health Canada CBA are in nominal terms, i.e., they have not been adjusted for inflation. However, the expected inflation rate in Canada currently is usually thought to be roughly 2%, the Bank of Canada's target rate, so the implied real discount rate in the CBA is 5%, still considerably higher than the 1.5% used by CADTH[26].

[26] The use of a 7% nominal rate in the CBA analysis implicitly gives much lower weight to the predicted impact in the later years where uncertainty is greatest.
The heading of Table 1, p 4 in the CBA suggests that the dollar figures that are cited in the document are in constant dollars, as does some of the language on p 10. However, the procedures described in some of the computer files that have been supplied to us suggest that the dollar figures are supposed to be in nominal terms, i.e., not corrected for inflation. In a revised version of the CBA, this issue should be cleared up.

Our second comment on the net benefit calculation concerns the way the costs and benefits to the various parties affected by the reform were aggregated to produce a measure of the net present value of the reforms to society as a whole. The main building block in this calculation was the estimated reductions in spending on patented drugs as a result of the reforms. These reductions essentially entered the calculation of the net benefit twice. First, they were treated as a benefit to consumers and payers; the discounted present value (at 7%) of these benefits over the period considered in the analysis was approximately $8.57 billion. Second, these same reductions were entered as a cost to the industry of $8.57 billion. Administrative and compliance costs of the new regulatory measures to the government and industry, were estimated as only $0.06 billion, meaning that total costs were estimated at around $8.63 billion.

The standard approach in cost-benefit analysis is to calculate the net benefit to society as a whole as the total benefits to all parties affected by an action, minus the total costs to all parties. Applying that principle to the above estimates, however, does not make sense: it would yield a small negative number as the estimate of the net benefit to Canada of the regulatory reforms.

Calculating net benefits in this way would not make sense because the reason why the PMPRB regulates drug prices is to reduce the incidence of "excessive" pricing. Although the meaning of "excessive" is not well defined in law or in the economic literature, it certainly ought to be thought of in such a way that if an excessive price is rolled back, there is a net gain to society. That is, the savings to the payers and the healthcare system should be weighted more

heavily than the corresponding reduction in the sellers' revenue when such a measure is evaluated from society's point of view. We return to this issue in Chapter VI.

The standard approach in the Treasury Board Guidelines to estimating the net benefit to Canada of a proposed action suggests a further reason why the predicted revenue losses to the pharmaceutical industry should be given less weight than the savings to patients and payers in present analysis: the revenue losses will largely be borne by the foreign nationals who own most of the shares in the multinational pharmaceutical companies. When a cost-benefit analysis is done from a Canadian perspective, only benefits and costs that affect domestic enterprises are supposed to be counted. The CBA document notes that the TBS Guideline refers to this principle (p 27 in the CBA), but explains that in the analysis of the PMPRB reforms it was decided to count the full value of the reduced industry revenue as a cost to Canada, even though 90% of the companies that report to PMPRB are MNEs.

We agree with the judgment that the reduced revenue of the pharmaceutical companies should not be considered irrelevant to the analysis, even if most of the revenue reduction affects foreign nationals. As discussed in Chapter II, the profits that the multinational pharmaceutical companies earn in Canada should be treated partly as Canada's contribution to the global financing of pharmaceutical R&D, and if we take unilateral regulatory action to reduce this contribution, other countries may think that we are not carrying our fair share and retaliate in ways that are costly to the Canadian economy. From a strictly Canadian perspective, it is the potential costs associated with such retaliatory actions by other countries that should be estimated when we try to decide whether stricter PMPRB regulation is in our national interest. If

the risk of retaliation is low because it can be argued that the prices that will be reduced were "excessive" to begin with[27], a cost-benefit analysis would assign less weight to the estimated reduction in the industry's revenue, increasing the likelihood that the analysis would predict a net benefit to Canada. Unfortunately, there is no agreed method to estimate the "net benefit" to Canadians from this broader perspective.

The CBA document did not take this approach to calculating an estimated net benefit to Canada. Instead, it included the full value of the expected revenue reduction to the pharmaceutical industry on the cost side. Other things equal, this would tend to bias the calculation of the expected net benefit to Canada in a negative direction.

However, any bias in that direction was more than offset by another item that was included as a final step in the calculation: what is referred to in the CBA document under the heading "Healthcare System" (Table 1, p 4), and later as "Public Healthcare Systems Benefits" (p 24). In this step, the estimated benefit from the reform package was augmented by assuming that each dollar that was saved by a public-sector payer (i.e., one of the federal and provincial programs that pay for all or most of the drug costs of certain population groups) would generate 3.3 dollars' worth of additional economic benefit. That is, while each dollar of estimated cost savings to individual patients or private insurance plans was included as one dollar on the benefit side in the calculation, each dollar that would be saved by a public plan was valued as an increase of the benefit side by 4.3 dollars.

[27] Using this logic, one might think of, the term "excessive" as applying to a price that contains an element of rent which is in some sense higher than that needed to induce the appropriate level of global pharmaceutical R&D.

Our strong recommendation is that this particular "multiplier" element of the calculation should be disregarded. Beyond a reference to an observed statistical correlation between health care spending and GDP in a study published in a little-known journal (CBA p 25), there is no explanation of the rationale for this adjustment. It accounts for the entire net benefit to Canada that the CBA predicts from the reform package (of $12.7 billion, in present value terms, over the 2019-28 period). This estimate has been quoted in the public debate about pharmaceutical policy (HESA p 84), even though, in our judgment, there is virtually no theoretical or serious empirical support for the calculation that produced it. It is our sense that on balance it is appropriate at this time in Canada to weigh the lost revenues (i.e. costs) somewhat less than the savings to payers (benefits).

The Sensitivity Analysis

The CBA recognizes that the forecasts of future drug expenditures, and the impacts of the new Regulations, are highly uncertain. As we noted above, it devotes several pages (31-34) to a sensitivity analysis that is designed to illustrate how wide the range of predicted outcomes could be (Graphs 3, 4, and 5).

In the literature on cost-benefit analysis, what is referred to as a sensitivity analysis usually refers to calculations that are designed to illustrate how the outcome of a given action or policy may vary, depending on the values of unknown parameters whose true values can only be estimated. Normally, in estimating ranges and distributions of possible outcomes of this kind,

the parameters that are allowed to vary are those that are considered as not being under the decision-maker's control (that is, parameters that are taken as exogenous).

When the policy or action that is evaluated involves a range of possible decisions or parameters that *are* controlled by the decision-maker, one can of course also estimate how sensitive the outcomes are to these (non-exogenous) parameter or decisions. However, a clear separation between these two types of calculation should be maintained, since they seek to answer questions that are conceptually different.

In the CBA of the proposed PMPRB reforms, the non-exogenous parameters and actions that should be considered as "controlled by the decision-maker" are not just those that are described by the changes in the language of the Regulations, but also those contained in the Guidelines. The discussion in this Chapter should make clear that the latter will be a major component of the overall changes in the regulatory process. Hence in future analyses by the PMPRB we think it would be very helpful to expand the sensitivity analysis to deal with the effects of different assumptions about the Guidelines, and these effects should be calculated for constant and given values of the exogenous parameters. As we read it, the present version of the document deals *both* with the uncertainty that results from the lack of precise knowledge about exogenous parameters (for example, with respect to the rate at which developments in biologics would lead to accelerated spending on drugs, and a reduced effect of generic substitution), *and* with the changes that would result from different assumptions about the future Guidelines. However, the very important distinction between the two has not been made clear. More discussion about the details in the assumed Guideline provisions would be welcome. Indeed, in

future versions of this analysis by the PMPRB, tests of sensitivity of the impact of the new factors to different applications of the guidelines would be very helpful

CHAPTER V

The PDCI Report's Re-analysis and Criticisms

In January 2018, following CG1 and HC's CBA becoming available, PDCI – Market Access Inc (PDCI) published a report (19) containing a critique of HC's analysis; the report is listed as being commissioned by IMC[28]. Part of it is devoted to what is referred to as a Re-analysis of the predicted impact on the pharmaceutical industry of the proposals, and a critique of the methodology used to produce the estimated net benefit to Canada. The PDCI report also discusses, in more general terms, what it considers important elements that were neglected in the CBA (especially the possible impact of the proposals on Canadians' access to new drugs), as well as the perceived shortcomings in the way the government had consulted stakeholders regarding these elements. It also raises the question to what extent the proposals would lead to a duplication of tasks that already are performed by other agencies, such as CADTH, INESSS, and pCPA.

The Re-analysis

The central component in the Re-analysis is a new estimate of the impact of the proposals on the revenue of the pharmaceutical industry over ten years. The nature of the new estimate, and how its methodology differs from that in the HC CBA, are discussed on pp 5-7 in the report,

[28] This initial report was supplemented with a deck on July 5 called a Re-analysis (20). We have considered both documents in making our comments in this Chapter.

and summarized in Figure 1 and Table 1[29]. The forecasts are shown to differ widely: In PV terms, the CBA estimate is $8.6 billion, while the Re-analysis puts it at $26.1 billion.

There are two principal reasons why the Re-analysis arrives at a number that is much larger. First, the PVs of the estimated impacts in the CBA are lower because they are based on a higher discount rate: 7% vs 1.5% in the Re-analysis[30]. Second, and most important, the Re-analysis predicts a much larger impact from the change in the Schedule from the PMPRB7 to the PMPRB12. The PDCI report does not produce independent estimates of the effects of the other elements of the proposals (the New Factors, and the Third Party Price Adjustments): the numbers in the entries referring to these elements in Table 2, p 7 in the PDCI Critical Appraisal (19), are the same of those in Tables 3 and 5, pp 19 and 24, in the CBA. That is, in performing the Re-analysis, PDCI simply used the CBA quantitative estimates of the impact of the new factors and 3rd party price adjustment reporting[31]. The only numbers that were independently recalculated by PDCI were those referring to the "Updated Schedule", and the line with this label in Table 2 has numbers that are much larger than those in Table 4 in the CBA, p 22.

Some information regarding the assumptions and methods underlying the new estimates of the impact of the schedule change can be found in a Box on p 5 in the report. Additional information has been made available to us in a deck dated July 5, 2018 (20).

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[29] Like the CBA paper, the PDCI paper assumes that the impact of the proposed regulations will fall on "new" drugs only. If this is not to be the case as seems evident from the PMPRB Modernization Paper (15) then the PDCI estimates will (like the CBA estimates) need to be redone.

[30] The HC 7% discount is the nominal discount rate suggested by Treasury Board Secretariat irrespective of market sector, the PDCI 1.5% is a real (inflation adjusted) rate.

[31] PDCI indicated that it was unable to independently assess the impact of the New Factors given the lack of information in the CBA report with respect to assumptions, methodology and calculations for the impact of the New Factors. However, EY's analysis of the impact of pharmacoeconomic factors (26) attributes a very large impact to this factor. We have not assessed the EY documents.

The starting point of the PDCI calculation was a baseline for total industry revenue which was computed by simply assuming (not unreasonably) that it would continue to grow at 2.6% per year from 2015. PDCI then compared publicly available price data from Canada and the PMPRB12 countries for the 110 top-selling drugs in Canada in 2016, and found that in that year, 24.5% of the drugs had a list price in Canada that was higher than the highest price in any of the other countries, while 67.3% had prices exceeding the median prices in the comparison group.

Using observed expenditure data for the different drugs, it was then calculated that if the prices on all drugs that were higher than the Highest International Price Comparison threshold were reduced to this threshold, industry revenue in 2016 would have been reduced by 3.5%. Performing the same type of calculation for the drugs whose Canadian prices were higher than the median in the PMPRB12 yielded a predicted reduction of 16.5%. Finally, it was assumed that 10% of the drug revenue in each year from 2019 to 2028 was for drugs that were newly introduced in that year, while the rest was for "existing" drugs, i.e. drugs that had been introduced prior to 2019.

The predicted expenditure reduction in each of the forecast years was then computed on the assumption that new drugs (those introduced after the proposals had come into force) would generate 16.5% less revenue than in the baseline, while revenue from "existing" drugs in each year would be reduced by 3.5%. Based on that logic, the predicted expenditure reduction R in a given year was then computed as $R = Y\,[\,x \cdot 0.165 + (1 - x) \cdot 0.035]$, where Y is projected baseline revenue and x is a coefficient that is 0.1 in 2019 and then grows by 0.1 in each successive year until it reaches 1 (100%) in 2028. In general, the annual numbers resulting from

this computation are much larger than those in the CBA. For example, for 2023 the PDCI analysis is $1.84 billion, while the CBA has $0.40 billion for that year.

In PV terms (using different discount rates), the total difference over ten years is dramatic: the CBA shows $2.8 billion while the PDCI figure is $18.5 billion. When combined with the estimates for the reductions in expenditure from the New Factors and the Third-Party Price Adjustments, the totals, in present value terms, are $8.6 billion in the CBA and $26.1 billion in the PDCI Re-analysis, the numbers we cited earlier.

As already noted, part of the reason for this difference is the lower discount rate that was used in the Re-analysis. Recalculating the present value of the total effects that are shown for each year in PDCI's Table 2, p 7, at a discount rate of 7% (the rate used in the HC CBA), we get a total that is almost $7 billion lower than the $26.1 billion estimated by PDCI at a 1.5% discount rate. However, the revenue reductions that PDCI predicts in each year as a result of the change in the schedule are so much larger than in the HC CBA that the present value of the total effect that PDCI would predict from all three elements together remains more than twice as high as in the HC CBA, even if one uses the same 7% discount rate in both cases.

The logic that was used in the Re-analysis to estimate the impact on industry revenue attributable to of the schedule change is itself not unreasonable, and the estimation procedure is clearly explained. But the calculations that it involved are likely to result in numbers that overstate the likely impacts, for several reasons.

First and most importantly, the estimates of the price reductions that would have had to be made if the price ceilings had been calculated from prices in the PMPRB12 schedule, were made via a comparison of *list* prices, in Canada and in the countries on the schedule. But the actual *transaction* prices that determine revenue are, on average, considerably lower than the list prices, and a given percentage reduction in the list price will not necessarily cause an equivalent percentage reduction in the average transaction price. Hence, the actual reduction in revenue is likely to be smaller, in relative terms, than the percentage reduction in list prices.

Second, the estimated percentage revenue reduction for new drugs is higher than that for existing drugs (that is, drugs that had been introduced in Canada before the new regulations came into force). For this reason, the PDCI estimates are relatively large in part because they assume that as much as 10% of spending each year is for new drugs (that is, the share of total expenditure that is attributable to drugs that had been introduced after the new regulations came into force would increase by 10 percentage points each year, as per the formula on p 55). In the HC CBA, this percentage is smaller, and either is empirically estimated (for Category 1 drugs) or assumed to be only 6.25% (for Category 2 drugs). In our view, the empirical basis for the fraction of revenues attributed to newly introduced drugs in a given year is likely to be closer to the HC estimate than to the PDCI estimate[32].

Finally, the estimate of the aggregate revenue reduction that is predicted to result from all three elements together in the PDCI is probably overstated to some extent because it relies on the HC CBA estimates of the effects of the elements other than the Schedule Change (that is, the New Factors and the Third-Party Price Adjustment). In the CBA, the latter effects were

[32] PDCI acknowledges that it would not be unreasonable to conduct sensitivity analyses with new medicines at 6.25% per year.

estimated first, before considering the impact of the Schedule Change. Had the estimates of the impacts of the other elements in the CBA been calculated *after* allowing for the effects of the Schedule Change, they would in all likelihood have been somewhat smaller. In the PDCI report, the effects of the Schedule Change are estimated first, so adding the effects of the other elements as estimated in the CBA will tend to produce a total that is overstated at least to some extent.[33]

While we appreciate the clarity and simplicity of the PDCI approach to estimating the impact of the change in the schedule from PMPRB7 to PMPRB12 on industry revenues from 2019 to 2028, our considered view is that this approach is likely to overestimate the actual nominal impact, at least if one assumes that the Guideline changes that would accompany the new Regulations were similar to those that were used in generating the CBA.

Other Criticisms

In addition to computing an alternative estimate of the reduction in revenue to the pharmaceutical industry that the proposals will cause, the PDCI report also criticizes other aspects of the CBA's methodology.

As noted in Chapter 4, we, like the PDCI, are highly critical of the CBA's use of a fiscal multiplier in estimating the net benefit of the proposals to Canada. Many of the PDCI reports other criticisms, however, are made with little or no appeal to established principles in cost-benefit analysis. For example, we believe that the analysis of the relation between Canadians'

[33] When the impact of one element of the reform is estimated last, it will be based on looking at hypothetical prices that already have been reduced by the application of other reform elements. When the impacts of the different elements are estimated in sequence, their relative magnitudes will therefore depend on where in the sequence they were calculated, at least to some extent.

access to new medicines and price regulation is not based on a well-established empirical relationship[34].

Finally, some of the report's criticisms regarding the lack of transparency in the policy development process, and of the lack of effective consultation, at times may seem excessively strident. Nevertheless, they do point to legitimate issues that should continue to be taken seriously in the ongoing consultation process. We also believe there is justification for some of the concerns the report raises with respect to the proposals leading to duplication of activities that already are being undertaken by other agents in the system. For example, while we strongly support the use of pharmacoeconomic evaluation as a valuable tool for payers when they make reimbursement decisions, it is less clear how it should be tailored to be a centerpiece in the toolkit that the PMPRB uses for price regulation.

[34] Notwithstanding PDCI's assertion that international launch sequencing based on price is a well-established industry practice.

CHAPTER VI

Summary and Conclusions

Introduction

As outlined in Chapter II, the role of the PMPRB is to protect consumers of patented pharmaceutical products from excessive prices charged by patentees during their period of monopoly provided by the Patent Act. Because purchasing of drugs in Canada is highly decentralized (unlike the situation in many other OECD countries with roughly comparable health care systems) the PMPRB plays a very important role as a counterweight to the pricing power given to patentees[35].

Current law and regulations do not provide a clear definition of "excessive" but rather instruct the PMPRB to provide guidelines as to what is "excessive" by referring to prices of drugs in seven comparable countries and to the price of comparable medicines already introduced in Canada. Over time, reliance on international price comparisons for new drugs has become more difficult as unreported actual transaction prices in other countries have increasingly diverged from the publicly available reported prices, which the PMPRB uses for purposes of comparison. For this reason, authorities in other comparable countries have put increased reliance on other factors in negotiating and regulating the prices of drugs in their jurisdictions.

Current regulations in Canada do not require that the PMPRB consider the pharmacoeconomic value of a drug or the ability of Canadians to pay in making its determination

[35] See Annex 1 for a comparison between Canada and other countries.

of an excessive price. This is unlike the situation in other countries with health care systems comparable to Canada where agencies responsible for purchasing and/or control of drug prices consider pharmacoeconomic value and ability to pay.

The Proposed Regulatory Changes

To modernize PMPRB's regulatory framework, the Government proposes not just to change the list of reference countries but also to specify by regulation additional factors that the Board should take into account to better reflect the broader perspective on what price might be judged to be "excessive", and to set out reporting requirements to enable the PMPRB to operationalize the new factors. These new factors together with the new list of comparator jurisdictions and improved price reporting are designed to give the PMPRB a broadened basis for determining the maximum non-excessive price for new drugs – a basis somewhat more comparable to that used in OECD countries with health systems similar to ours in Canada.

Other similar countries (e.g. UK, Australia) have moved towards closer integration among the agencies that are responsible for the purchasing and price regulatory functions, and government policy toward drug pricing in these countries is increasingly based on factors such as pharmacoeconomic analysis and impact on the health care system, with domestic and international price comparisons playing a diminishing role. The addition of the new regulatory factors to be considered by the PMPRB not only adds clarity to the meaning of "excessive" but brings the considerations used in drug price regulation in Canada more into line what is achieved by different mechanisms in jurisdictions with comparable health care systems.

Thus we judge that the introduction of the new factors, enhanced reporting requirements, and revisions of the schedule for international price comparisons is reasonable and that there is no good economic or conceptual reason not to proceed with the proposed regulatory changes.

In the analysis of the impact of the regulations which will be included with CGII, Health Canada could draw on the framework it established in the CG1 CBA, but should be much clearer on the working assumptions it has made about the PMPRB guidelines for implementation of the new regulations. However, following the gazetting of the new regulations, it is imperative that the PMPRB continues its process of consultation with stakeholders on the basis of further careful empirical analysis of the impact on prices and industry revenues of alternative formulations of the Guidelines.

The Empirical Analysis of Impact on Revenues

As requested in the statement of work (2) we have assessed, in Chapters IV and V of this report, the CBA analysis (3) and the PDCI analysis (19) of the impact of the proposed regulation changes on prices, industry revenues and payer expenditures. Both analyses were based on the assumption that the new regulations would focus on new drugs and have limited impact on prices of drugs existing in 2018.[36] If the intention is that many of the new features will apply to existing drugs as well, the impact on total pharmaceutical revenue is likely to be considerably higher, adding to the urgency of making new estimates before the new guidelines come into

[36] Although, as discussed in Chapter 4, the main forecast in the CBA provided for a schedule change effect on existing category 1 drugs as a result of "rebenching" (application of the MIPP to existing category 1 drugs.

force. In general, the impact of the new regulations on prices, expenditures and industry revenues will depend critically on how the PMPRB Guidelines are modified in order to operationalize the new regulations.

The analysis carried out by Health Canada in its cost-benefit analysis (CBA) was carefully done. The CBA made good use of recent data to project forward status quo baseline revenues and expenditures. As we indicated in Chapter IV, the way Health Canada modeled the impact of proposed regulatory changes was well done based on specific assumptions that were reasonable.

But the future is uncertain. There is a band of uncertainty around the baseline forecast set out in table 2 (especially in the later years). There is an even wider band of uncertainty around numerical impacts of the proposed changes set out in tables 3 through 5 in the CBA paper. The CBA recognizes this and provides a sensitivity analysis that shows some examples of how the estimated impacts would change under different assumptions. We think the sensitivity analysis provides a reasonable range of values of the baseline forecast and the impact of the proposed guidelines. However, we wish that the analysis had distinguished more clearly between the effects of truly exogenous parameters and the effects of assumed changes in the guidelines.

Turning to the PDCI-market analysis re-evaluation, the methodology it used was relatively straightforward. PDCI made a simple baseline projection with less detail than in that of HC, accepted HC's estimates of the impact of the "new factors" and the reporting requirements, but employed a totally different data set and analytical framework to estimate the impact of the change in the schedule of comparator countries. Like HC, PDCI also made

particular assumptions about how the new schedule would be operationalized. We believe that some assumptions – especially with respect to the impact of the median price of PMPRB12 on the realized actual transaction prices for new drugs in Canada – caused the PDCI estimates to be biased up. In addition, the statistical assumption that newly introduced drugs constitute 10% of industry revenue each and every year seems to be too high – and certainly higher than those estimated or assumed in HC's CBA. While we believe the PDCI estimates are likely to exaggerate the impact of the proposed changes on drug expenditures and on revenues of the industry, we note that these estimates would fall within the top end of the "plausible range" of impacts on future revenues set out in the CBA analysis, especially if a common 7% discount rate were used to determine the PV of the estimated impacts over ten years.

We assessed both the CBA and the PDCI analyses on the understanding that the new rules would mostly affect new drugs. However, the PMPRB has made it clear in the Modernization paper of June 25, 2018 (15) that tests based on the new factors and schedule could apply to <u>all</u> drugs, including existing drugs (as of 2018) in both categories 1 and 2. This evolution since the Scoping Paper in PMPRB thinking how the new factors, schedule, reporting requirements, and classification of drugs would be administered could substantially change the estimated impact on revenues and expenditures estimated in both the CBA and PDCI analyses. We have not been able to carry out re analyses on the basis of alternative assumptions about the Guidelines, so we cannot estimate what the impacts would be if analysis were done on the basis of Guidelines suggested in the June 25 Modernization Paper.

Further Empirical Analysis

In CGII we strongly suggest that Health Canada in the methodology paper accompanying the analysis make clear its precise assumptions about PMPRB's implementation of the new regulations. In the process of ongoing PMPRB consultations about the Guidelines to implement the new regulatory framework, we strongly suggest that the PMPRB fine tune the analysis of the impact of the proposed regulations using alternative ways to operationalize the new factors, the schedule, and the reporting requirements. With respect to the pharmacoeconomic value factor, we suggest that further analysis be done testing alternative threshold values. Cost utility analysis is in our view an appropriate tool for payers to use in establishing the maximum prices that they should be willing to pay on behalf of consumers, and it can also be helpful in deciding when a proposed price would be "excessive". However, as discussed in Chapter 3, while there is widespread agreement that CUA can be used as a flexible tool in payer/supplier negotiations, there is less agreement on the adaptations required to use CUA as a tool in price regulation. In any case, the choice of threshold maximum costs per QALY is critical to implementation of this factor. Going forward it is very important that Guidelines set out how these thresholds are to be established and which other agencies (CADTH, INESSS, etc.) might be involved.

As we argued in Chapter III, Canadians benefit from access to new medicines resulting from global R&D and hence should contribute a fair share to financing R&D through prices charged for patented medicines. Clearly, market size and relative GDP influence what might be considered a country's "fair share" of R&D financing and hence drug prices. There have been many suggestions in the literature as to how to use these factors and we have reservations about

any specific measure – including the one assumed in the CBA – to adequately define what is Canada's fair share. Measuring market size at the time of introduction of a new medicine is difficult and a matter of judgement; estimating the precise impact of the market size and GDP factor on aggregate future expenditures on patented medicines is even more difficult.

What is clear, however, is that the market size for a drug may certainly evolve over time as it becomes more widely used and/or off-label usage increases. Thus, when this factor is to be applied, in particular if it is to be used in "rebenching" the maximum allowable price, the impact on industry revenues depends critically on how market size was forecast initially, and how the regulated price should be impacted when actual sales deviate from the forecast. Going forward, consultations with stakeholders should examine the likely impact of alternative formulations of the Guidelines regarding market size on future revenues.

Finally we note again that the impact of change in the schedule from PMPRB7 to PMPRB12 depends critically on how the median international price is to be used in determining the MAPP. Since the median price in the new 12 countries is likely to be only moderately less than that in the original 7 countries in most cases, it is the use of the new median international reported price as a constraint on the Canadian regulated maximum price that is critical to the estimate of the impact on industry revenues[37]. Moreover, the estimated impact depends critically on the order in which this test and the test of the impact on the new factors is applied (and vice versa). Even though the value of the international comparison test in establishing the MAPP has become weaker over time as actual (unreported) transaction prices abroad diverge from reported

[37] Looking at average prices, the new PMPRB12 median country is Belgium with a relative price of .78 compared to Sweden, the median in the PMPRB7 with a median price of .89 (CBA table 6).

prices, nevertheless it is important that guidelines establish clearly how the new median international price is to be used to establish the MAPP.

Empirical Estimation of Net Benefits

As we have observed in Chapter IV, we believe that the regulatory changes might well yield a net benefit to Canada. But estimating how large that net benefit (or cost) is difficult because there is no well established methodology to do so. Among other things, it requires an assessment of the degree to which Canada is currently perceived as contributing its fair share to global R&D financing. If it is generally judged by our trading partners whose firms carry out R&D and benefit from Canadian patent protection that Canada already is contributing its fair share or more, then the cost of a dollar of patentee revenue lost could legitimately be assigned a lower weight than the benefit of a dollar saved by Canadian payers. In this situation, there can clearly be a net benefit to Canadians of reductions in ceilings on non- excessive prices as PMPRB implements the proposed regulations. The CBA analysis of the aggregate impact of the new regulations indicates that there will be a significant reduction in revenues and expenditures while at the same time not reducing Canadian prices below the median price in comparable jurisdictions. If other countries recognize this, they are less likely to engage in retaliatory measures that are costly to us, making it more likely that the proposed regulatory changes will yield a net benefit to Canada[38].

[38] See the discussion in the section on Calculating the Net Benefit to Canada in Chapter IV.

That said, there no agreed on economic methodology for estimating the size of the net benefit or cost. In the HC cost-benefit analysis, a dollar of reduced industry revenues is treated as an economic "cost" of the proposed changes while the same dollar of reduction in payments by public drug plans is multiplied by a factor of 4.3 in order to determine the economic "benefit" of the proposed changes[39]. Because, and only because, of this assumed "multiplier", the CBA produces the estimate of the gross PV of future benefits due to proposed changes of $21.2 billion ($3.0 billion annual average) quoted in Table 9 (p37) of the CBA. It is this procedure of multiplication of benefits that leads to the present value of "net benefits' of $12.7 billion ($1.8 average annual net benefit) quoted on page 8 of CG1. This estimate has been quoted in the public debate about pharmaceutical policy (HESA, p. 84) even though in our judgement, there is virtually no theoretical or serious empirical support for the calculation that produced it. Nevertheless, it is our sense that on balance, it is appropriate at this time in Canada to weigh the lost revenues (i.e. costs) somewhat less than the savings to payers (benefits). It is our assessment that the proposed changes to the regulations would yield a positive net benefit.

Concluding Comment

We believe the proposed regulations clearly provide an improved conceptual basis for the PMPRB to make judgements on the maximum acceptable product price for a new drug at the time it is introduced in Canada and that there is no reason to delay their introduction. However, estimating the actual impact of the proposed regulations on prices (and hence expenditures and revenues) depends crucially on the way that the regulations are operationalized through the

[39] This "multiplier" to reflect the "significant opportunity cost for the Canadian public healthcare system" has no basis other than a reference to a somewhat obscure 2013 paper.

Guidelines. In the consultations about the Guidelines that are now underway, it is imperative that the PMPRB provide empirical simulations of the different impacts that would arise under different scenarios for the Guidelines. We believe that the methodology that HC has used in the CBA analysis (i.e., a baseline forecast and analysis of 2010-2015 data as the basis for predicting future impacts) is adequate for this purpose as long as methodologic details are clearly articulated. Because the future is uncertain, it will never be possible to arrive at a precise estimate of the future impact. However, testing the empirical estimation against different implementation scenarios (Guidelines) and alternate baseline scenarios (relating to the types and quantities of drugs likely to be introduced over time) should provide comfort to both consumers and suppliers of patented medicines that neither will the impact on consumer expenditures be unreasonably small or the impact on industry revenues unreasonably large. It is in the interest of both producers (as represented by the IMC) and consumers (as represented by the PMPRB) to cooperate in building a transparent analytical model to test the likely impact of different variations of implementation guidelines.

APPENDIX

Drug Pricing in the U.K., Australia, and Europe

In this Appendix, we consider the question to what extent the proposals for modernizing PMPRB's role in drug pricing are consistent with the "approaches and considerations" that are used in the drug pricing process in other countries, such as the U.K., Australia, and some other European countries.

From the literature we have consulted, it is clear that in most of the world's high-income countries, the two main tools that are used by government to influence the prices of patented drugs are either some form of reference pricing, on one hand, and "value-based pricing" that draws on Health Technology Assessments (HTA), on the other. The term "reference pricing" can be used to refer either to the principle of regulating prices of new drugs with reference to existing domestic prices of drugs in the same therapeutic class (however that concept is defined), or with reference to prices of the same drug in other countries ("external reference pricing", or ERP). For HTA, the tool that increasingly dominates it is what we have referred to in the text as pharmacoeconomic evaluation, typically in the form of Cost-Utility Analysis that tries to estimate a new drug's ICER, expressed as a dollar figure per incremental QALY, and compare it to a previously established threshold value.

The literature also makes it clear that the increasingly common use of confidential discounts that are granted by the pharmaceutical companies as they bargain with payers over

prices, has made external price referencing less effective than it has been in the past. Accordingly, value-based pricing has gradually become a more important element in the drug pricing process in many countries. The proposals for modernization of PMPRB's role in Canada clearly involve elements that are intended as a response to the perceived ineffectiveness of external reference pricing in this country as well, and that would take us in the same direction as other countries in relying more on HTA.[40]

Drug Pricing in the U.K.

The example of extensive use of HTA in the drug pricing process that probably is best known to many people is the U.K., where NICE, the National Institute for Health and Care Excellence, has established itself as a world leader in that application of pharmacoeconomic evaluation in the form of CUA. Indeed, the U.K. is a bit of an outlier among non-US high-income countries in that it, in principle, makes no use of external price referencing in its drug pricing policy. Instead, this policy is based on HTA and implemented through a set of rules that seek to control the profits that the major pharmaceutical companies earn from operations in the U.K., and to control the National Health Service's total drug budget. Judging from available data, the approach seems to have been somewhat successful: on average, drug prices in the U.K. are close to the OECD median (9, p 16), and pharmaceutical expenditures as a share of total healthcare costs appear lower than in most European countries (30 p 350; 32 p 373).

[40] As an aside, it is worth noting that the proposed change in the list of comparator countries that is an important part of the reform proposals in Canada, have been observed in other countries as well (30 pp 353-4).

The U.K. does have legislation that provides for direct regulation of drug prices (the Statutory Scheme) and that includes external price referencing as a factor, but this scheme only applies to drugs that are sold by manufacturers that have not joined what is called the Pharmaceutical Price Regulation Scheme (PPRS), an agreement that has been negotiated between the Department of Health and the Association of British Pharmaceutical Industry (34 pp 8-9). Under PPRS, the prices of the drugs that these firms sell are not directly regulated, but have to be set in such a way that their reported profits from operations in the U.K. do not exceed specified limits; if they do, they have to lower prices in the future, and/or pay back some of the excess revenues they have earned.

In addition to controlling firms' profits, the PPRS also sets a cap for total spending by the NHS on branded prescription drugs. If that cap is exceeded, the firms actually have to make payments to the NHS to make up for the overspending. Such payments were made in 2017, when participating firms were required to pay the NHS the equivalent of 4.75% of their sales to the NHS (34 p 54). This provision effectively gives the NHS control over its total annual drug budget, which comes close to total national expenditures on drugs; in the U.K., every resident is covered by the NHS, and NHS coverage includes the cost of drugs (net of certain limited patient co-payments). The proposal that PMPRB should try to take account of the predicted impact of a new drug on provincial plans' drug budgets when regulating its price, may be considered a small step in the direction of giving it better control over aggregate drug spending in Canada. It is not clear, however, how effective it would be, since it would be applied in a system that is very different from the way drug costs are financed in the U.K.

The text of the PPRS agreement (which is valid for 5 years and will be re-negotiated at the end of 2018) states that the prices are expected to be "close" to the expected value of the medication, as established by NICE. The evaluations undertaken by NICE are highly influential in the decisions whether a drug will be included on payers' lists of covered drugs. In the U.K., the payers, technically, are the several hundred Commissioning Groups (CCGs) through which a large portion of the U.K. healthcare budget is administered. However, the CCGs are in principle required to fund drugs that NICE has estimated as cost-effective, meaning that its evaluation comes close to having the status of a reimbursement decision. There is no separate authority in the U.K. that is charged with negotiating prices with the suppliers, or even discounts or rebates; the CCGs are, in fact not allowed to seek discounts or rebates. However, when NICE evaluates a drug, it can negotiate a general discount (under a version of what is referred to as a Patient Access Schemes (34; p 20). Discounts negotiated in this manner are treated as confidential, meaning that they will not be made known to agencies in other countries that are collecting information on drug prices for external price referencing purposes[41].

[41] Funding decisions for orphan drugs and drugs used in the treatment for rare diseases are made by separate bodies (e.g., NHS England in that country).

Drug Pricing in Australia

Pharmacoeconomic evaluation also is a key element in the Australian model of drug pricing. In Australia, there is a universal national drug insurance plan, the Pharmaceutical Benefit Scheme (PBS) that pays most of the cost of prescription drugs for all Australians.

The PBS is managed by the federal Australian government, and listing decisions that determine the PBS's coverage are made by the federal Department of Health. Listing recommendations are made by a Pharmaceutical Benefits Advisory Committee, an "independent expert body" that, since 1988) has been required by law to take cost-effectiveness into account when making its recommendations (33; pp 7, 8). Before 2014, the PBAC was not responsible for negotiating prices with suppliers; instead, there was a separate agency called the Pharmaceutical Benefits Pricing Authority that was responsible for price regulation and could set prices, perhaps after negotiating with suppliers. In setting prices, the PBPA was supposed to consider a range of factors, including not only estimated cost-effectiveness but also prices of medicines in the same therapeutic class, cost information, prescription volumes, and prices of medicines in other countries. That is, the list of factors it was supposed to consider appears to be somewhat similar to those in the proposals for PMPRB reform.

In 2014, the PBPA was abolished and "price negotiations were integrated into the PBAC evaluation process" (33; p 8). If this new integrated agency is merged with the branch of the Department of Health that is responsible for listing decisions, Australia will then have a single agency that combines the functions that currently are carried out in Canada by CADTH, the

PMPRB, pCPA, and a range of individual payers. The list of factors that this agency is expected to take into account in setting or negotiating prices may look somewhat similar to that in the proposals for modernizing the PMPRB's role[42], but they will be applied in an institutional framework that looks very different.

Other European Countries; the Reporting Requirements

A recent survey of drug pricing in European countries adds to the evidence that HTA, in the form of pharmacoeconomic evaluation, "have become increasingly important" (34; p 351), and also that expected market size often is taken into account when negotiating prices. For example, there may be agreements stipulating that future prices will be adjusted according to actual sales volume. (31; p 358). There may also be reference to risk-sharing or "managed-entry" agreements in which there are provisions for reductions in prices if the anticipated improvements in health outcomes do not materialize to the extent that was originally foreseen. Similar language can be found in descriptions of the possible Patient Access Schemes that may be negotiated in the U.K. if a drug does not initially pass NICE's cost-effectiveness test for a positive recommendation (34; p 20), and in a description of what may happen as a result of the "post-market reviews" that the PBAC in Australia regularly undertakes after a drug has been in use for some time (33; pp 8-9). These provisions seem consistent with the idea of "re-benching" that is part of the proposed regulatory reforms in Canada.

[42] One noteworthy feature of the Australian system is that listing of any drug that is expected to lead to spending that exceeds AUS$ 20 million per year, will be considered by the federal cabinet. (33, p 8).

Discussions of drug pricing in other countries also provide support for the idea that government agencies involved in price negotiations or listing recommendations should have access to better information than they currently do, with respect to the discounts and rebates that determine the real net prices to payers, and with respect to other factors that influence pharmaceutical firms' net profits in a given country. IQVIA (34; p 25) refers to new legislation in the U.K. that will empower the government to obtain information about discounts and rebates "from all parts of the supply chain", while Vogler et al (31; p 367) cites Germany as an example of a country that has switched from regulation based on the traditional form of external reference pricing (i.e., based on list prices), to regulation based on real discounted prices. These features can be interpreted as international precedent for the enhanced reporting requirements that are part of the Canadian proposals.

Some Caveats

Not surprisingly, the examples cited in this Appendix show that other countries are wrestling with the same issues in drug pricing as those that have motivated the proposals in the PMPRB Regulations. In many cases, the measures they have taken or considered, especially with respect to the increased stress on pharmacoeconomic evaluation, are similar to the ones in these proposals.

But as we have emphasized in the text, the questions whether the ultimate outcome will be a regulatory process that is more or less like the more successful models among those that exist in other countries, will depend to a large extent on the Guidelines through which the proposals are implemented. For example, the supplementary documents we have seen suggest that the way the GDP and market size factors will be taken into account by the PMPRB will be through use of two very specific formulas (the Hollis and ICER models). We have not come across any suggestions that formulas of this kind have been used anywhere else; if they are indeed used, the outcomes in the Canadian market may end up looking very different from those in other countries, even if they are based on the same factors.

Moreover, it must be kept in mind that the U.K., Australia, and most of the European countries all have pharmaceutical financing systems in which regulation of prices is much more closely integrated with evaluation, payer-supplier negotiations, and listing decisions, than it is in Canada, where these functions remain somewhat fragmented. Changing the regulatory language so as to give the PMPRB a potentially more effective set of tools may be a valuable first step, but

in the long run, achieving closer integration among the agencies that are involved in the drug pricing process may be more important for achieving a system that properly balances the objectives of patient and payer protection against that of contributing Canada's fair share of global pharmaceutical R&D financing.

LIST OF DOCUMENTS CONSULTED

	TITLE
1	Canada Gazette 2: Regulations Amending the Patent Medicines Regulations - December 2017
2	Independent Assessment Proposal and List of Questions to Guide the Assessment – May 23, 2018
3	CBA: Health Canada Cost-Benefit Analysis: September 8, 2017
4	CBA Estimates: Summary & Methodology - (undated)
5	CBA Estimates: PMPRB Summary of the Methodology – updated July 12 and revised July 24, 2018
6	Health Canada: Assumptions and Preliminary Guidelines for Consultations – mimeo July 6, 2018
7	Material for Independent Assessment of CBA – mimeo July 9, 2018
8	Health Canada Presentation: Proposed Amendments to the Patented Medicines Regulations – December 2017
9	Health Canada Presentation: Cost-Benefit Analysis- January 2018
10	PMPRB Annual Report 2016
11	Health Canada: Basket of Comparator Countries – December 2016
12	PMPRB Guidelines Scoping Paper – December 2017
13	Health Canada Protecting Canadian From Excessive Drug Prices Consultation – May 2017
14	PMPRB Guidelines Modernization Discussion Paper – June 2016

15 PMPRB Framework Modernization – Consultation Document - June 25, 2018

16 PMPRB Presentation Framework Modernization – June 2018

17 PMPRB Steering Committee Terms of Reference – June 2018

18 PMPRB Working Group Draft Terms of Reference – June 2018

19 PDCI Critical Appraisal of the Cost-Benefit Analysis – January 2018

20 PDCI Re-Analysis - pp deck, July 5, 2018

21 IMC Submission: Regulations Amending the Patented Medicines Regulations – February 12, 2018

22 IMC Submission to the PMPRB – October 4, 2016

23 IMC Response to Health Canada – June 28, 2017

24 IMC/BIOTECanada Letter to Health Canada and ISED – April 20, 2108

25 Health Canada/ISED Letter to IMC/ BIOTECanada – May 31, 2018

26 EY Presentation HTA Factors Analysis – July 5 and 19, 2018

27 Compendium Policy Guidelines and Procedures - 2017

28 Deck presentation (Guidelines SC, 2nd Meeting, August 15, 2018

29

30 Babar, Zaheer-Ud-Din ed., "Pharmaceutical Pricing in the 21st Century", Springer 2015

31 Vogler, Sabine, and Jaana Martikainen, "Pharmaceutical Pricing in Europe", Ch. 19, pp 343-69 in Babar 2015

32 Morrison, Emma E., and Daniel J. Webb, "UK Health Technology Assessment and Value Based Pricing", Ch. 20, pp 371-87 in Babar 2015

33 Vitry, Agnes Isabelle, Loc Thai, and Elizabeth Roughead, "Pharmaceutical Pricing Policies in Australia", Ch. 1, pp 1-23 in Babar 2015 [Vitry et al 2015]

34 "Pharmaceutical Pricing and Reimbursement Concise Guide: UK", December 2017, pp 1-70 [IQVIA 2017]