



Alexion Pharma Canada Corp.

E-Mail: [PMR-Consultations-RMB@hc-sc.gc.ca](mailto:PMR-Consultations-RMB@hc-sc.gc.ca)

June 28, 2017

**Patented Medicines Regulations Consultations**

70 Colombine Driveway  
Tunney's Pasture  
Mail Stop 0910, Floor 10  
Building Brooke Claxton Building  
Ottawa, ON K1A 0K9

Dear Sirs:

**RE: Response to Consultation on Proposed Amendments to the Patented Medicines Regulations**

Alexion Canada Pharma Corp. (Alexion) submits these comments in response to Health Canada's recent publication, *Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations* (the "Regulatory Proposals"). Alexion, a company dedicated to research and development of life-transforming therapies for patients with devastating ultra-rare diseases, submits to the Minister, the Department, and all Canadians its frank and, we hope, useful comments on the Regulatory Proposals.

**1. Executive Summary**

The purpose of the Regulatory Proposals is reflected in the title: to lower perceived "excessive" drug prices in Canada. Regrettably, the Regulatory Proposals make no mention of the predictable and certain negative consequences the proposals, if adopted, will have on availability in Canada of drugs for patients with rare and ultra-rare diseases.

As a manufacturer and marketer of medicines for patients with ultra-rare diseases, Alexion views the approach taken in the Regulatory Proposals as duplicative of existing provincial programs, misguided as public policy, and unconstitutional under Canadian law. In our view, the Regulatory Proposals will decrease the availability in Canada of medicines to treat rare diseases—in short, it will harm Canadians.

The *Patent Act* currently provides that the determination whether a drug price is "excessive" turns on comparing prices of the medicine under review with the prices of "comparable" medicines in the same therapeutic class or with the price of the same medicine sold in other countries. In other words, an excessive price is defined *in relation to* other relevant prices,

taking efficient advantage of the myriad factors—efficacy, patient tolerance and adherence, physician behaviour, and the cost of research and development—that determine market prices. Whether a medicine is “*expensive*” is irrelevant—and, in fact, undefined—under this regime: the question is whether the price is *excessive*, as that term is used in the *Act*, based on the prescribed comparisons.

The Regulatory Proposals will completely transform this comparative process, by purporting to introduce “...new, economics-based price regulation factors that would ensure prices reflect Canada’s willingness and ability-to-pay for drugs ...”. This is price regulation at its purest and has nothing whatever to do with whether or not a patentee is abusing the monopoly created by a grant of patent.

Rather than recognizing the special challenges facing development of innovative drugs for ultra-rare diseases and providing incentives to develop such drugs, the Regulatory Proposals actually target rare disease drugs for “...a higher degree of regulatory scrutiny...”. Because it is deliberately untethered to the costs of rare-disease drug development, and the economics of rare-disease drug distribution, this direct regulation of rare-disease drug prices will lead to reduced availability in Canada of medicines to treat rare diseases.

Patients in Canada with ultra-rare diseases already face a challenging environment. New life-saving drugs are either not introduced into Canada at all, or their availability is delayed compared to other countries. Provincial governments and the federal government are extremely reluctant, or unwilling, to fund rare disease medicines, and for this reason the pathway for obtaining funding is complex, lengthy, and unpredictable. Unlike other countries, and despite previous policy initiatives, Canada has taken no steps to introduce legislation or programs designed to encourage development and availability of so-called “orphan drugs”. The Regulatory Proposals will, in fact, have the consequence of further discouraging invention in Canada, or introduction into Canada, of medicines for rare diseases. This approach actually defeats the stated policy of accessibility to medicines for Canadians, contradicts the practices and policies of comparable countries, and could have devastating consequences for patients in Canada who suffer from rare or ultra-rare diseases and who will be deprived of life-saving medicines.

Apart from these foreseeable consequences, the Regulatory Proposals introduce such an array of different factors that the proposed system will likely produce arbitrary and unfair results. The Regulatory Proposals will confer unlimited discretion upon the Board to set and vary prices. The new system continues troublesome features of the current scheme and introduces three practices and concepts—pharmacoeconomic analysis, size of market, and GDP—that will lead to even less certainty and consistency, a higher regulatory burden for patentees, and greater risks of *retroactive* asset confiscation.



In effect, the Regulatory Proposals seek to give the Board more authority to directly regulate and control drug prices, as opposed to its statutory authority to prevent “excessive” pricing. Instead of regulating directly and transparently, however, the Regulatory Proposals seek to implement “new methods” and “reforms” characterized as science, but which in fact give the Board unrestricted power to defeat a manufacturer in any pricing dispute. This approach is the antithesis of both science and fairness. The proposals will give rise to numerous future proceedings relating to prices of which the Board may disapprove at any given time.

Finally, a primary target of the proposed policy changes appears to be manufacturers of drugs for rare and ultra-rare diseases. But the changes ultimately will affect some of Canada’s most vulnerable citizens: those who, but for the treatments offered by these manufacturers, would not be treated and in many cases would not survive.

## **2. Constitutionality of Regulatory Proposals**

The Regulatory Proposals are unconstitutional. Parliament does not have legislative competence to impose macroeconomic justifications like “GDP per capita,” or a Canadian patient’s “willingness to pay”, as a basis for price regulation. Nor does Parliament have authority, under the *Patent Act* or any other legislative power, to determine whether a given patient receives adequate value for money from one medicine relative to another. Quite apart from the unconstitutionality of such an approach, these determinations are much better left to a treating physician in the first instance than to a federal body.

The Regulatory Proposals focus only on Health Canada’s, and the Board’s, concerns with drug prices in Canada. There is no suggestion of any broader consultations with Innovation, Science, and Economic Development Canada about the impact of the regulatory changes on patent policy, including patent protection and reduction in the value of patent rights in Canada. These are extremely important considerations given Canada’s domestic commitments to fostering innovation in Canada and Canada’s international treaty obligations to safeguard patent and property rights. Furthermore, if implemented, the proposals could induce manufacturers of medicines for rare and ultra-rare diseases to remove the products from the Canadian market.

## **3. Understanding the Complexities of Rare & Ultra-rare Disease Research & Development**

The Regulatory Proposals focus on “high cost” treatments, which often include therapies for

patients with rare and ultra-rare diseases.<sup>1</sup>

It is important that Health Canada, healthcare providers, policy makers, clinicians, patients, and the general public understand the difficulties entailed in getting rare disease treatments to market.

The impact of ultra-rare diseases on patients, their families, and society is profound. Many of these diseases are severe, chronic, progressive, and carry a high mortality rate. Ultra-rare diseases present unique challenges. Typically, few researchers or companies investigate these diseases. When developing treatments, there is little prior science or technical knowledge. Often, there are no regulatory pathways available to deal with the difficulties of demonstrating effectiveness of a treatment for diseases with so few patients.

Most successful new medicines for the treatment of rare diseases are preceded by *many* costly failures that lead nowhere. The 'winners' must pay for the losers and fund a generous return to investors who risk vast sums to support highly speculative ventures like rare disease drug development and still leave the manufacturer with sufficient capital to pursue research and development of its 'next generation' products.

By definition, ultra-rare diseases affect fewer than 20 persons per million in the general population. A correspondingly small number of clinical trial participants are available. Setting up clinical trials for ultra-rare diseases is costly, complex, and time-consuming. Substantial resources are required to establish a sufficient number of worldwide clinical trial sites given the small number of patients eligible for enrolment, and without certainty that each site will, in fact, be able to contribute to the trial.

Alexion alone is currently conducting clinical trial programs that involve establishing hundreds of clinical trial sites around the world. In comparison, clinical trial patients with more common diseases like diabetes, which affects 49,000 per million in the general population, can generally be recruited in a small number of readily accessible domestic sites.

Treatments for ultra-rare diseases are subject to largely the same regulatory and clinical evaluation process and requirements as treatments for common diseases, and attract the associated costs. Extraordinary risk is borne by companies to develop treatments for the very few patients suffering from ultra-rare diseases about which little is known and for which no effective treatments exist.

---

<sup>1</sup> See the Regulatory Proposals, page 7: "In addition to paying high relative prices, all payers in Canada are struggling with a dramatic increase in the number of high cost drugs on the market"; at page 8: "Central to this position is the recognition that patented drugs have differing potential to exert market power and charge excessive prices. This potential is largely shaped by the characteristics of the market for each drug, such as the availability of comparator products and the size of the patient population ... It is proposed that drugs be evaluated against such characteristics to determine the relative risk of excessive prices. Drugs with higher potential to exert market power would face a higher degree of regulatory scrutiny..."



As a result, it is important that any changes in current policy do not discriminate against patients with rare and ultra-rare diseases by imposing requirements that discriminate against high per patient-cost medicines. Regrettably, many of the Regulatory Proposals carry a significant risk of serious negative effects on patients living with ultra-rare diseases. These changes are described in detail below.

#### **4. Supporting Innovation for Research into Treatments for Rare Diseases**

It is important to keep the effectiveness of treatments for patients with ultra-rare diseases on the Canadian healthcare system at the centre of the discussion. As a result of funding and policy choices by both the federal and provincial governments, there are very few treatments available in Canada for patients with ultra-rare diseases compared to the total number of medicines for rare diseases available worldwide. Spending by public drug plans on rare disease treatments currently accounts for less than two percent of total drug budgets. If Canadian jurisdictions were to cover *all* ultra-rare disease treatments available worldwide (excluding treatments for rare cancers) between now and 2018, the *total* cost of covering all rare disease patients across the country would not exceed four percent of provincial and territorial drug spending<sup>2</sup>. Spending on all prescription drugs—including those for ultra-rare conditions—accounts for approximately nine percent of provincial and territorial healthcare budgets; thus, the total cost of covering all available ultra-rare disease treatments would account for only about 0.4% of the total healthcare budget.<sup>3</sup>

#### **5. Discrimination Against Patients With Rare Diseases**

Patients with ultra-rare diseases do not choose their diseases, but they depend on the same healthcare system as everyone else in Canada. Patients should not be penalized or discriminated against simply because the diseases from which they suffer are not “common.” This is especially so when the provision of equitable access to ultra-rare disease treatments accounts for a small proportion of overall spending on drugs in Canada and only a miniscule fraction of total annual healthcare spending.<sup>4</sup>

Other jurisdictions—most notably the United States and the countries of the European Union—have accepted the importance of helping ultra-rare disease patients by providing specific incentives to spur drug research and development for rare diseases. The US *Orphan Drug Act* (enacted by Congress in 1983) encourages research and development in the field of rare diseases by providing enhanced orphan drug exclusivity to companies willing to assume

<sup>2</sup> The Budget Impact of Drugs Treating Rare Diseases in Canada: A 2007-2013 MIDAS Sales Data Analysis. Victoria Divino et al. Oral Presentation at the 2015 CADTH Symposium.

<sup>3</sup> Canadian Institute For Health Information Report on Prescribed Drug Spending in Canada, March 2014.

<sup>4</sup> Devino et al, 2015.

the financial risk of pursuing treatments for life-threatening, ultra-rare conditions. Government and private payers support and facilitate this research and development by paying for treatments and supporting the small patient populations. In the European Union, the sponsors responsible for these medicines benefit from incentives like waivers of the considerable government fees for regulatory reviews and approvals or a 10-year market exclusivity from date of introduction to the market.

Canada has no such legislation and is thus 34 years behind the US in developing a policy to foster development of medicines to treat rare diseases. Health Canada's attempt to develop an Orphan Drug Regulatory Framework has been halted by the current Health Minister. Canada has therefore missed an opportunity to link innovation and support for patients with ultra-rare diseases. Alexion shares BIOTEC's concern that Health Canada's proposed regulatory modifications are harmful to the government of Canada's Innovation Agenda led by the federal Department of Industry, Science and Economic Development. The goals of two important federal government departments are clearly at odds with each other.

## **6. Research & Development Spending**

In the Regulatory Proposals, Health Canada raises the concern that the existing regulatory framework has not achieved its goal of encouraging research and development spending by patented medicine companies in Canada.<sup>5</sup> This is based on an analysis taken from the PMPRB's Annual Reports. The method the PMPRB uses to quantify R&D spending—limited to SR&ED eligible expenses—recognizes only the smallest fraction of investments by companies with products on the market. The Board's approach completely ignores significant investment that is not SR&ED-eligible, and does not include any of the R&D being conducted by companies working to bring innovation to the Canadian market. These R&D investments are the backbone of Canada's innovation ecosystem.

In this respect, Alexion's 2011 acquisition of Enobia Pharma Corp., the largest biotech acquisition in recent Canadian history (at \$1.1B), had a tremendously positive effect on Canada's biotechnology ecosystem. Specifically, Alexion assumed and supported a significant Canadian clinical trial program for asfotase alfa, an enzyme replacement therapy used to treat the ultra-rare and life-threatening condition, hypophosphatasia (HPP), in which infants are unable to properly mineralize and grow bone. The incidence of HPP is about 1 in 100,000, but increases to 1 in 2,500 live births in the Mennonite population. HPP is therefore a rare disease of particular significance in Canada. R&D resulted in a therapy being developed in Canada. Yet, none of the investment made by Alexion to bring a therapeutic innovation developed in Canada to the global market is considered by the Board to constitute R&D. Moreover, and especially for rare diseases, by their very nature there can only be a

---

<sup>5</sup> See page 12 of the Regulatory Proposals.



small amount of clinical research conducted in any one country, because there are so few patients in each country. Current Canadian funding policies lack a clear, likely, and predictable funding stream for such products and act as a significant disincentive to undertaking R&D in Canada.

## **7. Putting Patients First**

It is Alexion's hope that Health Canada will engage with patients living with ultra-rare diseases through this consultation process. If Health Canada's goal is to create a pricing environment that ignores the economic factors involved in bringing ultra-rare disease treatments to market and focuses solely on achieving the lowest possible price, it simply will not be feasible for companies over the long-term to offer rare disease treatments in Canada. As a consequence, these small and overlooked patient populations will have limited or no access to life-saving medicines. Furthermore, a process for regulating the maximum price that can be charged for rare disease treatments already exists. This maximum allowable price serves as a backstop by which Canadian payers—private and public—have developed sophisticated and robust mechanisms for obtaining favourable prices through negotiations. In the case of the provincial, territorial, and federal governments, a buying group has been formed through the pan-Canadian Pharmaceutical Alliance (pCPA). Private payers also obtain favourable prices through the implementation of co-pay plans which are usually offset by the manufacturers.

## **8. Canada Is a Challenging Market**

Canada is a challenging market for companies seeking to deliver first-in-class treatments for patients with life-threatening, ultra-rare diseases. These treatments must navigate the "common drug review" of the Canadian Agency for Drugs and Technologies in Health (CADTH), a process that makes no provision for the reality that ultra-rare disease treatments have small clinical trial sizes, or that randomized double-blind studies cannot be conducted on patients with life-threatening conditions. Only 34% of drugs for rare diseases<sup>6</sup> receive positive CADTH recommendations, and a positive recommendation is generally required to enter negotiations with the pCPA.<sup>7</sup>

If an ultra-rare disease treatment does receive a positive recommendation, there is no special pathway through the pCPA to obtain funding or to ensure timely access for patients. In fact, ultra-rare drug listing applications and negotiations often take longer than non-innovative,

---

<sup>6</sup> Reimbursement of Drugs for Rare Diseases through the Public Healthcare System in Canada. Where Are We Now? Devidas Menon, Derek Clark and Tania Stafinski. *Healthcare Policy*. 11(1) August 2015. 15-32.

<sup>7</sup> Health Technology assessment of new drugs for rare disorders in Canada: Impact of disease Prevalence and Cost, Rawson, *Orphanet Journal of Rare Diseases*, (2017) 12:59

“me-too”, drug applications. This means that patients must wait even longer for access to what is usually the only approved therapy to treat their disease.

The impact of price regulation regimes on the availability of drugs in different jurisdictions is well-established: price regulation delays the launch of new and innovative drugs generally.<sup>8</sup> This effect is amplified for drugs intended for ultra-rare diseases, where the costs per patient are greater and the affected population smaller.

## 9. Alexion’s Experience with the Board

Alexion entered the Canadian market in 2009 with the introduction of Soliris (eculizumab), a Health Canada-approved treatment for an ultra-rare disease, Paroxysmal Nocturnal Hemoglobinuria (PNH). Alexion carefully followed the Board’s Guidelines in setting the price of Soliris. Even though the price has never changed, and the Board confirmed in 2010 and 2011 that the price was “Within Guidelines”, Alexion has been required by the Board to defend its price in a lengthy and costly hearing because international exchange rate fluctuations affected the *perceived* cost of Soliris, when compared with prices in other countries. These exchange rate fluctuations were beyond the company’s control and had no impact on the price being charged for Soliris either within or outside of Canada.

The Board has taken the additional step of attempting to retroactively change the permissible price of Soliris, which the Board approved after introduction in 2009 when it categorized Soliris as a breakthrough medicine. This approach, combined with the extensive attention paid to “high cost” drugs in the Regulatory Proposals, signal to industry that both the Board, and now Health Canada, actively seek to discourage innovation in Canada, particularly as it relates to ultra-rare diseases.

In the interest of supporting rare disease patients and Canada’s Innovation Agenda, Health Canada should give careful consideration to how it addresses treatments for diseases with the smallest patient populations. Patients with rare diseases require such support because investor, and therefore research, dollars, tend to go to where the greater returns are. Unsurprisingly, this tends to be diseases which have large numbers of potential patients, not small numbers.

The critique of the specific elements of the Regulatory Proposals below, demonstrates that these proposals will not promote or encourage innovation in Canada for ultra-rare disease treatments; to the contrary, the proposals will likely *discourage* innovation in Canada.

---

<sup>8</sup> See I. Cockburn, J. Lanjouw and M. Schankerman, “Patents and the Global Diffusion of New Drugs,” American Economic Review 2016, 106(1): 136–164, at p. 136.



## 10. Feedback to Regulatory Proposals

### *Critique of Assumptions Made in the Regulatory Proposals*

#### *(a) Price Increases*

The central assumption of the Regulatory Proposals is that increases in spending on drugs over time is problematic and must be addressed by price regulation. This assumption is stated in the Executive Summary, which notes that “the emergence of higher cost drugs, such as biologics and genetic therapies ... are putting increasing pressure on drug spending”. The increase in spending is overwhelmingly driven by biologics that are intended for treatment of relatively common conditions;<sup>9</sup> The Regulatory Proposals do not, however, distinguish between drugs for relatively common conditions and drugs for rare or ultra-rare diseases. This regulatory focus on unit price is explicitly aimed at drugs for rare and ultra-rare diseases. In the section entitled “Canadian Drug Prices”, the Regulatory Proposals state:

“In 2005, there were 20 drugs on the Canadian market with an annual average cost per patient of \$10,000 or more. By 2015, that number grew more than five-fold, to 124. That number represents nearly one-quarter of public and private drug plan costs but less than 1% of their active beneficiaries.”

The focus on increasing expense overlooks that treatments have emerged for rare and ultra-rare diseases that simply did not exist before. The alternative, in the past, was that the small number of “active beneficiaries” suffering from rare diseases lacking any effective treatment simply suffered or died. It is unreasonable to expect the total amount of payment for drugs to remain static over time when great strides have been taken in the use of drug therapy to expand into entirely new areas where past available treatments were ineffective or non-existent. The development of medicines for rare and ultra-rare diseases is of necessity more expensive than the development of therapies for common diseases. If the prices are subject to the same cost-benefit economic factors as medicines for common diseases, few rare disease drugs would ever be invented or marketed.

In the Regulatory Proposals, Health Canada alludes to a supposed increase in drug prices, but does not explore the causes of that increase. No evidence is cited that drug discovery has become cheaper. There is also no evidence that pharmaceutical company profits in Canada have increased. The drive to reduce prices in response to an increase in costs appears to be an effort to force Canadian pharmaceutical suppliers to absorb cost increases, rather than

<sup>9</sup> Such biologics are now facing competition from “biosimilars”, previously referred to in Canada as “subsequent entry biologics”, which are essentially generic versions of biologics. See Health Canada, Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs.

payers, who in the case of drugs for rare or ultra-rare diseases are mainly provincial governments. There is no explanation for how this type of pressure is fair or consistent with the *Patent Act*. Nor is there any mention of the real risk that the approach could lead to even fewer ultra-rare disease medicines being made available to Canadian patients. While claiming to be motivated by “consumer protection”, the effect is to lower prices for public or private payers because provincial governments, not individual patients, pay for ultra-rare disease medicines.

The authors of the Regulatory Proposals claim that Canada’s drug prices are rising and are “among the highest in the world.” They attribute these supposed trends to the “absence of reform” in the manner in which drug prices are regulated in contrast to other countries.<sup>10</sup> The authors make no effort, however, to separate real changes in drug prices from either: (a) changes in the exchange rate of the Canadian dollar for foreign currencies; or (b) changes in the Canadian price level (“inflation”). These macroeconomic fluctuations have been substantial over the period under discussion.

In addition, the authors make no effort to compare the same basket of drugs across countries. Indeed, they cannot do so: because drugs are introduced later in countries in which patent protection is less valuable and the countries that appear to have the lowest priced drugs on average also have the least availability of new, high-priced, drugs.<sup>11</sup> No effort has been made to ensure that in conducting its analysis Health Canada (or the PMPRB) have confirmed, or even investigated, whether high-priced drugs available in Canada are also available in other countries. This would be the only reasonable method by which to compare the prices that consumers pay in each country.

Canadian policy makers have a choice: to provide for the funding of available drug therapy for rare and ultra-rare diseases, or to have the introduction of such therapies to the Canadian market delayed or thwarted entirely.

## **(b) Price Regulation**

A second assumption in the Regulatory Proposals is that the Board’s purpose is price regulation rather than to prevent patent abuse. This assumption is clearly revealed in the section entitled, “Consultation Details”: “Affordability and sustainability considerations fall within the PMPRB’s regulatory purview”. The assumption is further stated in the section entitled, “Limitations of the current framework”, where the Regulatory Proposals observe

---

<sup>10</sup> Regulatory Proposals, p.4.

<sup>11</sup> I. Cockburn, J. Lanjouw and M. Schankerman, “Patents and the Global Diffusion of New Drugs,” *American Economic Review* 2016, 106(1): 136–164.



that the current framework is merely based on price comparisons and not on “additional tools”:

“It does not consider whether the price of a drug reflects its value to patients or other relevant factors that influence drug prices in different markets such as market size or the relative wealth of a country ...”

The reason that the current framework does not consider “affordability”, “sustainability”, and related “additional tools” is that the drafters of the current framework understood, and at least attempted to work within, the limitations of a federal regulatory scheme applying to activities within the legislative competence of the provinces. The original notion behind creation of the current system was to encourage innovation by increasing length of patent protection for drugs; balance was achieved by creating mechanisms to prevent “patent abuse”. The system was never intended to create a regime of outright price regulation. Price regulation by the federal government in a particular market is unconstitutional. Price regulation in a particular market falls within property and civil rights and can only be regulated by the provinces. The federal government has always alleged that the current system is a legitimate extension of its power to regulate “patents”. The changes to the system outlined in the Regulatory Proposals undermine that characterization and will likely be subject to legal challenge.

From a purely economic viewpoint, the worst mistake in the Regulatory Proposals is confusion of the regulation of prices with the regulation of quantities. If a manufacturer sets a price that is too high by a cost-effectiveness measure, the buyer’s solution (in this case, the provinces and private health plans)—as in every other market—is not to purchase the drug. That decision properly signals to the manufacturer that its price is not justified by a drug’s benefits relative to alternative treatments. This signal is, of course, sent millions of times per day in all markets, and it is the basis on which manufacturers continuously re-evaluate their pricing decisions. The quantities that result are the response to those pricing decisions; quantities cannot be determined independently of pricing.

In effect, the Regulatory Proposals require the Board to presume to know the correct quantities of each medicine that should be sold, and then to instruct the manufacturer on the price to charge for those quantities. But the Board is not a patented medicines quantity review board. It has no knowledge, authority, or competence to determine what a quantity should be. The provinces may incorporate treatment options into their funding/reimbursement criteria in an attempt to ensure that only patients who are likely to benefit (or benefit most) are prescribed a given medicine, taking into account a specific drug’s price and treatment profile. Such efficient and informed decision-making should be encouraged. But such decisions are made as quantity responses to existing prices. They are not the basis for choosing new or different prices. Moreover, the decisions are better made

by an informed physician or payers, not in an administrative process that does not involve application of medical expertise.

Notably, the Regulatory Proposals do not explain how conflicting and/or changing cost-effectiveness evaluations would be treated. Suppose that the Board decides that drug A is priced “too high,” given its benefits relative to drug B, and orders a 10% price reduction. In response, drug B’s manufacturer reduces its price by 10%, to maintain the previous relative price ratio and, one presumes, relative market shares. Relative to this new price, the price of drug A is again “pharmacoeconomically” too high. The Board has no basis for determining the “correct” market equilibrium in the face of these pricing dynamics. That is because the Board cannot set pharmacoeconomically correct prices in the first place.

The larger point is that the Regulatory Proposals have confused protection against “excessive” prices with setting “correct” prices or “correct” costs to payers, neither of which is within the Board’s competence or legislative authority. It is, of course, a circular argument that any price that is not “correct” must be “excessive.” Since the Board cannot determine what a correct price is, linking correct prices to “excessive” prices simply invites more arbitrary determinations.

## 11. The Irrelevance of the Board

A third assumption in the Regulatory Proposals is an implicit concern about the relevance of the Board in the face of provincial ‘buying power’ over “actual” drug costs must be remedied by legislation. The source of this concern is well-known and stated in the Regulatory Proposals: the vast majority of drug spending, particularly for so-called high-cost drugs used to treat rare and ultra-rare diseases, is made by provincial government reimbursement through publicly-funded drug schemes. Provincial payers do not necessarily pay publicly-listed prices for drugs but use their considerable bargaining power to extract unit price reductions, rebates and other financial concessions that reduce drug costs through confidential “listing agreements” with manufacturers.

This places real control over drug prices and actual treatment costs with the provinces. The provinces bargain with manufacturers, either directly or through mechanisms like the pan-Canadian Pharmaceutical Alliance (pCPA)<sup>12</sup>. The significant provincial involvement is consistent with the constitutional structure of Canada’s federal system.

These provincial mechanisms both reduce the Board’s relevance (as noted in the Regulatory

<sup>12</sup> The pCPA conducts joint provincial negotiations for drug reimbursement “real” costs: that is, the total cost after any unit price discount, “rebate” and/or other concessions.



Proposals) and render the proposals in the Regulatory Proposals redundant. If implemented, the proposals will result in a multiplicity of reviews, with a cost-effectiveness review undertaken at the federal level (by the Board), at the joint provincial level (by CADTH and the pan-Canadian Oncology Review), and at the provincial level (by entities like INESSS and similar committees or bodies in other provinces). The Board will supplant direct provincial price negotiation in determining, at the national level, the relative value of a drug to patients.

To further complicate matters, if rebates and other concessions provided in product listing agreements affect the list price, these benefits cannot be kept confidential. There are good reasons why payers like Canadian provinces would want to keep such information confidential. Other payers (whether private or publicly-funded) which, individually, lack the bargaining power of the Canadian provinces will use that data to demand the same rebates. This means that the proposals, if implemented, will likely have the perverse effect of compelling manufacturers to refuse to offer concessions to the provinces. In global terms, Canada is a small market. If its actions will harm a manufacturer's ability to conduct profitable business in other—larger—markets, then a rational actor will sacrifice the smaller market.

## 12. “Relative Risk”

The authors of the Regulatory Proposals employ language like “risk analysis” and “relative risk” (an epidemiologic term) purportedly as a justification for the regulation of medicine prices. Medicine prices are not, properly speaking, “risks” at all. They are the results of deliberate choices made by manufacturers in response to market conditions, based on the attributes of a medicine and available alternatives, in response to patient demand. In contrast, a risk arises from an unpredictable set of events over which no one has control.

Ironically, should these Regulatory Proposals be adopted, “risks” would arise, not from the manufacturer of a patented medicine, but from the Board itself. The risks would involve unpredictable and unsound price decisions that would limit or prevent accessibility of drugs, particularly rare disease drugs, to patients in Canada. The Regulatory Proposals increase the scope and magnitude of such risks exponentially, particularly for manufacturers of drugs for rare or ultra-rare diseases. One rational and entirely predictable risk management strategy is for a manufacturer to elect not to sell a medicine in Canada. If patients in Canada want that medicine, then arrangements will have to be made to purchase it (in local currency in a country in which it is sold) and to import it into Canada.

### 13. Lack of Concern Over Transition

Alexion does not agree with the thrust of the Regulatory Proposals for all of the reasons canvassed above. Even if it did, there remain additional problems.

For example, the Regulatory Proposals contain no mention of how the regulatory change will be implemented, or the potential impact on drugs already regulated under the current system. The prices of drugs currently "not excessive" could change to being "excessive". No warning, or analysis, is provided about the impact the change will have on the industry. The issue is simply not mentioned.

There are two areas of concern: (1) whether the legal change is intended to have retroactive effect, meaning that the Board could claim "excess revenues" going back years for drugs not previously deemed excessive; and (2) the destabilizing impact of unpredictable price changes moving forward if the Regulatory Proposals are adopted.

Seeking "excess revenues" retroactively is manifestly unfair. It punishes manufacturers who have complied in good faith with existing law.

The more complex issue is the destabilizing effects of forcing price changes based on a system that is highly complex and unpredictable. In the past, the Board, in making changes to its Guidelines, has been careful to provide reasonable transition provisions. For example, when the Board first introduced the "highest international price comparison test" in 1993,<sup>13</sup> the Board stated:

The Board recognizes that the current prices of some drug products exceed the prices in all other countries but comply with the current Guidelines. In such cases, the following transitional provisions will apply ...<sup>14</sup>

Revised regulations, should they be adopted, must carefully include adequate transitional provisions to enable manufacturers to comply without disruptions, based on the same logic that the Board previously followed when making major changes to the Guidelines.

### 14. Critique of Use of New Factors

The suggested new factors in the Regulatory Proposals, if adopted, move the Board to a pure price control scheme, which is both unconstitutional and duplicates existing provincial mechanisms. Statements like "taking into consideration 'willingness and ability-to-pay' of

<sup>13</sup> PMPRB Bulletin, September 1993, Issue No. 12, at p.3.

<sup>14</sup> The transition provisions were, in summary, that the Board would not commence proceedings if "appropriate action" was being taken to ensure that the price would comply by January 1, 1996, through price freezes or reductions



payers” reveals both the new focus on price control and duplication of function. Particularly in the case of drugs for rare and ultra-rare diseases, the “willingness to pay” function is already performed by the provinces, who reimburse the cost of the majority of such products, and make such determinations without regard to federal regulation. The provinces determine whether new drugs are to be reimbursed in face-to-face negotiations with manufacturers based on their own pharmacoeconomic evaluations, guided where applicable by CADTH’s input.

For all manufacturers, the introduction of these new factors explicitly increases regulatory complexity, uncertainty, and the potential for arbitrary decisions. While complex, the existing system is, at least, based on valid comparisons that are, when actually applied by the Board, predictable. The proposed system contains both the existing comparison-based tests and completely new and different factors, like benchmarks established through reference to cost per quality-adjusted life year (QALY) and the size of the market.

If the established comparative tests are complex, adding many new countries to the basket of comparators multiplies the complexity. It is difficult to see how such complexity, and so many determining factors, can produce predictability and not lead to increased regulatory burden, uncertainty, and the real risk that new medicines will not be introduced on the Canadian market, or that introduction will be substantially delayed.

## **15. Pharmacoeconomic Evaluation**

As Alexion understands the Regulatory Proposals, the PMPRB would use a fixed cost per QALY threshold, apparently consistent with the CADTH approach, as the definition of excessive price. This proposal ignores that a drug’s unit price is not the same as a drug’s cost and that any specific cost per QALY threshold is a complex political and economic decision appropriate for those who prescribe or pay for a medicine. Further, if CADTH’s cost per QALY determinations are somehow to be simply upheld by the Board as the maximum permissible price, then this renders the Board redundant and the pCPA irrelevant.

Making treatment or access decisions based on an implicit or explicit cost per QALY threshold is not appropriate for rare and ultra-rare diseases. This measure of cost-effectiveness is generally not used by authorities in other countries to assess drugs used to treat orphan conditions because of the low prevalence of rare diseases and small market size. It is well understood and recognized, that drugs used to treat orphan diseases have to be priced at a higher level based on market factors and the difficulties inherent in quantifying cost-effectiveness thresholds for rare diseases. Some countries, like the United States, have developed specific legislation that provides incentives for the development of rare disease drugs. Other countries, like the United Kingdom, have developed unique review processes and standards applicable to therapies that treat ultra-rare conditions. While some provinces

have developed processes to assess the ‘value’ of orphan drugs, Canada does not have orphan drug legislation and no Canadian entity, including CADTH, has established a specialized review and approval process to deal with the cost-effectiveness of orphan drugs. Indeed, the Regulatory Proposals ignore Health Canada’s long-awaited orphan drug initiative.

Even if cost per QALY thresholds were an appropriate tool for a price comparison authority, the effect of inappropriately applying a cost per QALY threshold used for drugs for common conditions to drugs for rare and ultra-rare conditions is obvious: if used, rare disease drugs will *never* be found to be “cost-effective”. By definition, on a per-patient basis, rare diseases drugs will always be more expensive to develop and to purchase.

Use of a new “pharmacoeconomic” factor has the significant potential to prevent Canadians from receiving new medicines. Indeed, the use of such a measure may have the perverse effect of: forcing Canadians to purchase drugs for ultra-rare diseases outside Canada; importing the drugs via the Special Access Program; or even to move to countries where they can receive treatment.

## 16. Size of Market in Canada and Other Countries

The “size of market” factor appears designed to provide a mechanism to force drug prices lower if the market size for the drug is large (so as to result in “rationing”) or if the drug price increases after launch:

“Since monopolies are protected from new entrants, prices tend to remain unaffected from subsequent fluctuations in market size. Seeing that firms are assumed to set their introductory prices at a profitable level to recoup initial investment, a subsequent exponential growth in the market size should align and correct prices downwards to a comparable level. Failure to do so could suggest that the original price, for an expanded market, is now excessive.”

For rare and ultra-rare diseases, the reverse ought to apply: the very small size of the market for such medicines ought to result in *greater* leeway on pricing. The Regulatory Proposals, however, ignore this self-evident truth. If an important goal is to keep medicines for rare diseases available to Canadians, then the Regulatory Proposals will defeat this purpose and will, instead keep such medicines *off* the Canadian market.

The demand for market size data in the Regulatory Proposals demonstrates the authors’ failure to appreciate basic market economics. First, by “market size” the authors appear to mean ‘the size of the target patient population.’ Accepting that definition, this is, in other words, a quantity. It is not the basis for choosing a price. More fundamentally, it is a quantity that depends on the price; the price does not depend on the quantity.



Furthermore, the “market size” is not even a fixed number. Market size is: (a) unknown in most cases; (b) subject to change with additional innovation, and the development of complementary or substitute treatments; (c) the subject of marketing and other efforts to influence demand; and (d) is an endogenous factor (because whether a patient is “in the market” depends, in part, on the price charged by the manufacturer).

The authors of the Regulatory Proposals offer ambiguous definitions relating to measurement and economic significance of “market size,” and in particular the relationship between market size and price. The ambiguity creates a substantial risk that use of such a variable to guard against “excessive” prices will lead to arbitrary pricing outcomes. The approach will also deter the availability of such medicines in Canada.

## **17. Gross Domestic Product in Canada**

Gross Domestic Product (GDP) and per-capita GDP are not useful measures in determining whether the price of a drug for a rare or ultra-rare disease is “excessive”. Canadian consumers do not pay for rare disease drugs directly. The cost is borne by public or private insurers. No individual could afford even the least costly of such medicines. The determination of how much to spend on rare and ultra-rare patients is based on shared or pooled risk and not the individual circumstances of a particular patient. GDP and per-capita GDP cannot possibly be relevant factors in determining whether or not a medicine price is excessive.

### ***Answers to Consultation Questions:***

- 1. Do you agree that a pharmacoeconomic evaluation is an important factor for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should the evaluation be considered?**

This factor should not be used to evaluate medicines for rare and ultra-rare diseases. Rare diseases and the medicines used to treat them are, by their very nature, unamenable to the application of traditional cost-effectiveness analyses. Adding this as a consideration, without distinguishing between medicines for common diseases and medicines for rare and ultra-rare diseases, has the potential to eliminate rare disease medicines from the Canadian market.

- 2. Do you agree that the size of the market for the drug in Canada and other countries is an important factor for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should the size of the market be considered?**

Market size and market structure should be considered by payers in negotiating the cost of drugs for rare and ultra-rare diseases.

3. **Do you agree that Canada's GDP and GDP growth are important for the PMPRB to consider when determining whether a drug is priced excessively? If so, how should GDP be considered?**

GDP and GDP growth are irrelevant considerations for rare and ultra-rare diseases because individual patients do not pay (see discussion above). Reimbursement for the cost of such drugs is based on decisions of public or private insurers and based on collective or pooled risk. For public payers, prices are negotiated at the provincial level.

4. **Are there any other factors that should be considered by the PMPRB when determining whether a drug is priced excessively? How should the factor(s) be considered and what information should be required from patentees?**

No. Alexion does not believe the authority granted to the PMPRB under the *Patent Act* is constitutional.

#### ***Critique of Amending the List of Countries Used for International Price Comparisons***

The Regulatory Proposals include proposals to reconfigure the list of countries to which Canadian prices should be compared. The stated rationale for this reconfiguration is to take account of Canada's "ability and willingness to pay." Yet the proposal is to drop countries to which Canada routinely compares itself (e.g., the US and Switzerland), and to add countries, like Spain and South Korea, that are much different from Canada.<sup>15</sup> This change appears designed to drive down prices, not by analyzing the price that a manufacturer charges in Canada, but by arguing about whether a Canadian patient in Kelowna is more similar to an American patient in Spokane, a Spanish patient in Seville, or a Korean patient in Seoul. The results will be unpredictable. Moreover, unpredictability can be expected to increase over the life of the drug, as macroeconomic trends diverge and as Canada selects other countries to which to compare itself.

In the preamble to this section, the authors of the Regulatory Proposals complain that the use of patents has not resulted in any expected gain in R&D:

... the percentage of R&D-to-sales by pharmaceutical patentees in Canada has been falling since the late 1990s and is at a historic low. By comparison, and

---

<sup>15</sup> According to the International Monetary Fund figures for 2016, South Korea's per-capita income is 81% of Canada's; Spain's is 78%.



despite Canada having among the highest patented drug prices, industry R&D investment relative to sales in the PMPRB "7" countries is on average 22.8%, versus 4.4% in Canada.

As already described, this conclusion is based on the Board's own figures, which artificially and narrowly define R&D in a way that excludes vast swaths of R&D and investment actually undertaken in Canada. The definition used by the Board does not include R&D done by companies that do not already have a patented medicine or by companies for which research is coordinated from abroad and performed (in whole or in part) in Canada. As described above, Alexion's own experience with Enobia demonstrates how artificially limiting and arbitrary the regulatory definition of eligible "Canadian" R&D is.

In short, the federal government has established by regulation an extremely narrow and restrictive measure of success in this area, and now proposes further restriction on the basis that, by the artificial and restricted measure it has itself established, "success" was not achieved.

In the specific context of drugs for rare and ultra-rare diseases, research is spread out over many jurisdictions based on the necessity of obtaining sufficient subjects to complete the required clinical studies. Only in those cases where the rare disease in question is found in clusters (for example, where it is a rare genetic condition) will R&D be focused in one geographic area.

The most notable change in the list of countries is elimination of the United States. This makes no sense, geographically or economically. The United States is Canada's closest neighbour and the economies of the two countries share many similarities. Failure to compare drug prices to the US for those drugs where the non-excessive price is established by the highest international price test will create significant risk of parallel importation into the US from Canada. This is a risk that applies to all medicines, but is of special concern to manufacturers of medicines for orphan diseases because the numbers of patients in any country are so small. A manufacturer of a widely-used medicine may be able to absorb and tolerate some loss of revenue to a less profitable geographically contiguous market, but where the numbers of patients is extremely small (as is so with rare and ultra-rare diseases), even a handful of such cases may tip the balance against supplying the less profitable market. As a result, manufacturers will be extremely reluctant to launch new products in Canada, particularly products for rare or ultra-rare diseases. Finally, a concern with multiplying the number of countries is that it increases regulatory burden and increases the risk of exposure to currency fluctuations in application of the highest international price test.

*Answers to Consultation Questions:***1. Are there other countries that should be considered in revising the Schedule?**

The United States and Switzerland should remain on the schedule, for the reasons described above.

**2. Are there other criteria that should be considered in revising the Schedule?**

The number of comparator countries should be limited. Increasing the number of comparator countries increases regulatory burden, ignores dissimilarities between Canada and other comparators, and greatly enhances the risks of distortions based on currency fluctuations.

**3. Please provide any other comments you may have on the Schedule of comparator countries.***Reducing Regulatory Burden for Generic Drugs with a Patent**Answers to Consultation Questions:***1. Do you agree that patentees of generic drugs, i.e. drugs that have been authorized for sale by Health Canada through an ANDS should only report information about the identity of the drug and its price in the event of a complaint or at the request of PMPRB?**

As a research-driven, innovative company, Alexion has no concerns with the creation of a mechanism specific to generic drugs. Given Alexion's concerns about constitutional authority, however, there are serious concerns raised about to how a federal body like the Board can regulate prices of a good for which there are no Canadian patents.

Alexion reiterates that a specific mechanism for drugs for rare and ultra-rare diseases ought to be incorporated into the proposal.

*Critique of Modernizing Reporting Requirements for Patentees*

The pharmacoeconomic evaluation factor based on a cost per QALY threshold should not be used for drugs for rare and ultra-rare diseases.

The Regulatory Proposals state the following concerning the cost utility analysis required of patentees:



This information would be as consistent as possible with the information required by CADTH's Common Drug Review, pan-Canadian Oncology Review and l'Institut national d'excellence en santé et en services sociaux (INESS).

It makes no sense to require patentees to simply submit information required by CADTH, the pan-Canadian Oncology Review, and INESSS. Through this proposal, it appears that the Board will in effect *replicate* the analysis conducted by these organizations, with all the attendant risks of inconsistent results. There is no reason for a federal price comparison body to attempt to do exactly the same job as is already done by various provincial organizations. Moreover, the Board lacks the specialized expertise of these other organizations.

The estimated medicine 'uptake' information will naturally be highly speculative and prone to a significant margin of error. This is particularly the case with rare and ultra-rare diseases, whose frequency in the population is random and unpredictable given the low sample size. If a discovery that double the expected number of Canadians with a certain ultra-rare condition treated by a newly-introduced innovative drug forces a price decrease, will the discovery that half the expected number of Canadians with a certain ultra-rare condition permit a price increase so that the innovator can recoup its investment in its innovation? The proposed system will lead, in the case of such drugs, to significant price fluctuations and so to uncertainty and risk.

Moreover, there is no possibility that such information could be provided in a consistent manner. This requirement is vague and potentially burdensome.

(a) There is no agreed-upon definition of a "pharmacoeconomic evaluation"—other than merely copying what was undertaken by other organizations (which may not be consistent with each other).

(b) Even if there were an agreed-upon definition of "pharmacoeconomic evaluation", evaluations change constantly as the result of: approvals for additional indications; approval and withdrawal of competing medicines; development of complementary and/or substitute treatments; changes in the price of and reimbursement for hospital stays and other services; and changes in all market prices that are made in response to these market changes.

(c) Because these conditions and prices differ by country, the evaluations also differ by country.

(d) Finally, evaluations differ by patient: for some patients, one drug is "pharmacoeconomically superior" to another. Sometimes an "inferior" drug is selected after a patient has not responded to, or cannot tolerate, a "superior" drug. For any individual

patient, the question comes down to the treating physician's assessment of the therapeutic gains to be had from different alternatives at any given point in time.

In essence, the Regulatory Proposals require a real-time description of market innovation and competition as a condition for maintaining approval of a medicine's price. The Board is already challenged by the existing factors, which can create difficult determinations, for example, when prices appear to change based on fluctuating exchange rates or price inflation. Accurate processing and evaluation of market innovation and competition, even if the information were available, would lead to further unpredictability and possession of the information is no guarantor of "non-excessive pricing."

***Answers to Consultation Questions:***

**1. Is the information sought in relation to the new factors relevant and sufficient?**

For the reasons stated above, the information is irrelevant in the case of drugs for rare and ultra-rare diseases.

**2. Is this information generally available to patentees?**

The information submitted to CADTH, the pan-Canadian Oncology Review, and INESSS would be available. Information will not be available for countries other than Canada.

The information concerning estimated uptake would be highly speculative in the case of drugs for rare and ultra-rare diseases. Such speculation is unsuitable as a basis for binding pricing decisions.

***Critique of Providing Information Related to Third Party Rebates***

Requiring the reporting of discounts or rebates offered to third party payers like provincial governments is problematic for many reasons, described below.

***Answers to Consultation Questions:***

**1. Are there any reasons why patentees should not be required to disclose to the PMPRB information?**

There are many reasons why requiring patentees to disclose rebates and discounts negotiated by provincial payers does not make sense.



Given that many other jurisdictions base their pricing decisions on international comparisons, companies doing business in Canada will be extremely reluctant to offer discounts or rebates should those benefits prove not to be treated as strictly confidential.

The notion that such information would be adequately protected by the privilege found in section 87 of the *Patent Act* is doubtful, for three reasons: (1) the Board presumably wishes to base pricing decisions on this information, and so it will be reflected in the decisions the Board ultimately makes; (2) the section 87 privilege does not apply to information revealed in the context of a hearing before the Board which requires patentees to demonstrate the grounds required to exclude the public to keep information disclosed during a hearing confidential; and (3) it is unclear whether such information in the hands of the Board would be accessible via a federal access to information request.

The result will be that companies doing business internationally will be more reluctant to offer benefits in Canada if there is a significant risk that the information will be disclosed through compliance with the Board's regulatory requirements.

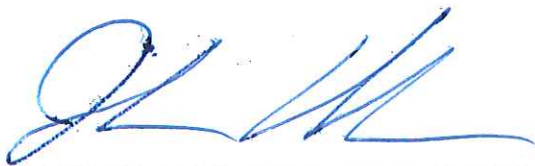
There is also significant doubt about the value of knowing the amount of domestic Canadian rebates. To make comparisons with international prices, the Board would also have to know the value of rebates offered to other countries. Companies would naturally be reluctant to reveal such information as a condition of access to a relatively small market like Canada.

...

Alexion would be pleased to elaborate on issues raised in this submission, and would be willing to make a representative available during the consultation process.

Yours very truly,

Alexion Pharma Canada Corp.  
per:

A handwritten signature in blue ink, appearing to read "J. Haslam", is written over a horizontal line.

John Haslam  
President and General Manager