CANADIAN PKU AND ALLIED DISORDERS INC.
PCU et MALADIES APPARENTÉES CANADA INC.

Written Brief of

Canadian PKU and Allied Disorders

To : Standing Committee on Health

Re : Study of Guidelines of

Patented Medicine Prices Review Board

November 6, 2020

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Recommendations

Recommendation 1: If the government must implement the new regulations and guidelines, they do so incrementally so that impacts of the individual elements can be properly assessed.

Recommendation 2: That the government produce meaningful case studies to demonstrate how the guidelines and regulations will change the Canadian pricing environment, how drugs for rare conditions will be affected, and what the Government believes success looks like.

Recommendation 3: That the government identify benchmarks and performance targets to be able to establish the success / failure of the regulatory and guidelines changes

- *Number of new medicines approved in Canada compared to top performing countries*
- *Timing of drug approval submissions in Canada compared to top performing countries*
- *Clinical trials conducted for new medicines in Canada*
- *Patients enrolled in clinical trials for new medicines in Canada*

Recommendation 4: That the government establish a program to collect, monitor, and report on the measures established in Recommendation 3.

Recommendation 5: That the government include the patient community and clinical researchers in the processes for Recommendations 3 & 4.

Recommendation 6: That the government undertake and publish a review to evaluate whether these regulations and guidelines have a disproportionate negative impact on women and mothers. The regulations and guidelines specifically target drugs that treat high-impact conditions and so-called high cost drugs. Caregiver burden falls predominantly on women and mothers.

Recommendation 7: That the government establish a funding mechanism for public-interest interventions by patient groups involved in the drug review and evaluation process in Canada.

Contents

Background

The Patent Act and Patented Medicines Regulations establish the PMPRB and provide the framework for identifying a *maximum non-excessive* ceiling price (wholesale) for "patented drugs".

The Guidelines explain the policies and procedures that the PMPRB normally applies in reviewing the prices of patented medicines sold in Canada.

Under the old regime, Canadian introductory prices are in line with international levels, but as drug markets mature, foreign prices decline relative to Canadian levels. Prices in the United States are markedly higher than in Canada and also in the other PMPRB7 markets for both newly introduced medicines and patented drugs in general[1].

New Regulations were published in August 2019 to come into force January 1, 2020 (after COVID delay).

The new Regulations:

a) Changed the list of comparator countries. Two high priced countries (USA and Switzerland) were removed and several lower priced countries were added (Australia, Belgium, Japan, Netherlands, Norway and Spain). The list was changed to include countries that "constrain free market pricing for medicines" through policy measures and to be better aligned with median OECD prices[2].

b) Introduced "economic factors" to be considered by the PMPRB - Pharmacoeconomic value; Market size; and Gross Domestic Product (GDP).

The new guidelines explain how the PMPRB will put the new regulations into practice.

The new guidelines establish the median of the comparator countries (designed to reflect the median of the Organization for Economic Cooperation and Development (OECD) as the absolute maximum for any patented drug price in Canada.

Every other guideline, rule or factor reduces the allowable maximum price below the median of the OECD.

[1] See PMPRB *Meds Entry Watch, 2015 to 2018 – for example* *http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1307*

[2] http://canadagazette.gc.ca/rp-pr/p1/2017/2017-12-02/html/reg2-eng.html

Who We Are

CanPKU

Canadian PKU and Allied Disorders Inc. (CanPKU) is a non-profit association of volunteers, first organized in 2008. We are dedicated to providing accurate news, information and support to families and professionals dealing with phenylketonuria and similar, rare, inherited metabolic disorders.

CanPKU has a membership of about 300 and represents 2,500 Canadians living with PKU plus their families.

PKU (phenylketonuria)

PKU is a rare, genetic disorder of metabolism which threatens the human brain and affects approximately 1 of every 15,000 babies born in Canada.

PKU patients lack the normal functioning of the one enzyme in the liver (called phenylalanine hydroxalyze) needed to turn phenylalanine (phe), an amino acid in protein, into another amino acid, tyrosine. This results in an accumulation of phe in the blood which crosses into the brain where it is neurotoxic, causing various degrees of mental deficiency and neurological issues.

Due to universal Newborn Screening Programs begun in the 1960s, almost all patients in Canada are diagnosed and started on lifelong therapy within a couple weeks of birth and are able to avoid the more serious mental defects associated with untreated PKU. However, a late-diagnosis can mean that some brain damage occurs before the proper treatment was implemented.

PKU is treated first by a severe restriction in the intake of all forms of natural protein – at least 80%. In fact the degree of protein restriction is incompatible with life. Hence the need for PKU therapy.

Our Treatments

The original way to treat PKU was to eat a special, highly restrictive medical diet under medical supervision that strictly limits foods containing phenylalanine. It also includes consuming several times a day a special prescribed medical formula with zero phe that provides the essential amino acid Tyrosine and other amino acids. Medical PKU formulas and foods are funded by all federal, provincial and territorial governments/government drug plans. While the medical formulas and foods are regulated by Health Canada for restricted access, they are not issued Drug Information Numbers and as such are outside the jurisdiction of PMPRB.

Individuals need to rigorously track and record everything that is eaten or drunk. This is essential for both the meal-to-meal, day to day management of the disorder, and as a reference to determine what has caused a high or low blood-phe level or a low Tyrosine level. For PKU children, this task falls to parents, and includes tracking what is and is not eaten at home, daycare, school, or when visiting family, neighbours or friends.

PKU Drug intervention

One drug has been approved in Canada for the treatment of PKU. Health Canada approved sapropterin dihydrochloride (Kuvan) for PKU ten years ago, in April 2010, as the first new treatment for PKU in 60 years. The saga of Kuvan after Health Canada approval is testament to the inability of the government drug “system” to adequately address the needs of Canadians with rare disorders.

Based on this unfinished Kuvan odyssey, after more than ten years, we submit there is a reasonable basis to fear the new guidelines under the 2019 PMPRB Regulations will make things worse for patients including PKU patients.

The USA Food & Drug Administration in 2018 and the European Medicines Agency in 2019 approved the second drug for PKU. We are left to wonder when, if ever, will it be available in Canada?

Two companies have started clinical trials of gene therapies which hold the prospect of a cure for PKU.

There are no clinical trials in Canada for these gene therapies and there were none for the second drug for PKU. This is a reasonable basis for deep concern.

Our Concerns

CanPKU and other patient advocacy organizations have made it clear that the new Regulations and Guidelines as proposed create a significant risk of delaying or reducing the availability of new medicines in Canada. The government has tacitly admitted this fact by exempting therapies and vaccines for COVID-19 from PMPRB rules. That was the right thing for this government to do. What about new drugs and vaccines for other diseases?

Canada's patient community has a clear goal - a regime that facilitates the introduction and availability of a comprehensive range of medicines, with the ability for patients to access medically necessary medicines in a timely manner. We don't believe the PMPRB regulations or guidelines help deliver that.

CanPKU filed comments in response to the proposed and revised guidelines[3] highlighting the fact that the draft Guidelines do not seem designed to prevent excessive pricing – but rather to help manage the expenditures of public drug plans.

The regulations and guidelines go too far:

- Too many new elements that will make it difficult to determine specific effects of any individual change
- Absence of clear sense of "how low is low enough"
- Unique Canadian application of Health Economic tools
- Emphasis on the "health care system" perspective, and ignoring the individual patient
- Someone decided the middle of the OECD was the right place for Canada as a start point for price negotiations

The risk to patients with unmet needs is that the changes will make the Canadian market less attractive as a destination for new medicines. This includes the idea that drug developers will seek regulatory approval later than in other countries, or not at all. It also includes the idea that companies will test fewer medicines in clinical trials in Canada – if they don't expect they will be marketed.

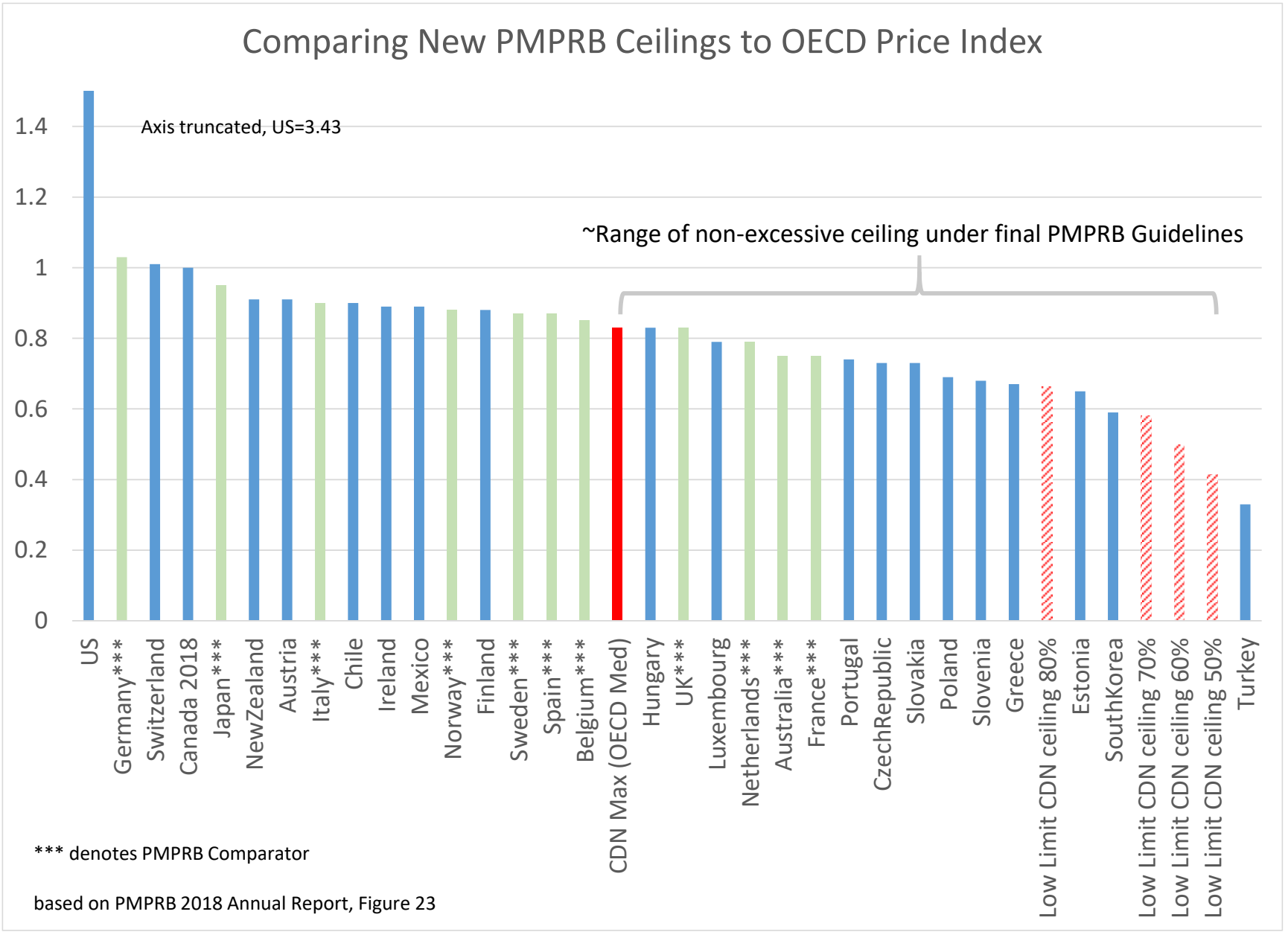
[3] Both CanPKU comments are attached for reference

Health Canada and PMPRB have dismissed these risks at every turn with statements such as “some countries with lower prices have new medicines at around the same time as Canada”. What they fail to acknowledge is that most of those countries are in Europe, and have the benefit of a common, single regulatory approval under the European Medicines Agency. When a drug is approved for the most lucrative market in Europe, it has approval for 29 European countries with markets having a population of 450 million. That is more than 12 times the size of the Canadian market.

The new guidelines establish the median of the comparator countries (designed to reflect the median of the OECD) as the absolute maximum for any patented drug price in Canada. Every other new guideline, rule and factor reduces the allowable maximum price below the median of the OECD.

Health Canada and PMPRB have gone to great lengths to lower allowable drug prices to reflect what the public health system is “willing to pay” and what they are “able to pay”. Nothing in these changes has provided any certainty or incentive for any part of the health system to ultimately provide access to medicines at these prices. For Canadian patients this is a double whammy: the price levels might mean that medicines don’t come to Canada, and even if they finally do, the health system still might not cover them.

FIGURE 1


Comparing New PMPRB Ceilings to OECD Price Index
Axis truncated, US=3.43
~Range of non-excessive ceiling under final PMPRB Guidelines
1.4
1.2
1
0.8
0.6
0.4
0.2
0
US
Germany***
Switzerland
Canada 2018
Japan***
NewZealand
Austria
Italy***
Chile
Ireland
Mexico
Norway***
Finland
Sweden***
Spain***
Belgium***
CDN Max (OECD Med)
Hungary
UK***
Luxembourg
Netherlands***
Australia***
France***
Portugal
CzechRepublic
Slovakia
Poland
Slovenia
Greece
Low Limit CDN ceiling 80%
Estonia
SouthKorea
Low Limit CDN ceiling 70%
Low Limit CDN ceiling 60%
Low Limit CDN ceiling 50%
Turkey
*** denotes PMPRB Comparator
based on PMPRB 2018 Annual Report, Figure 23

CANADIAN PKU AND ALLIED DISORDERS INC.
PCU et MALADIES APPARENTÉES CANADA INC.

February 14, 2020

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Re: PMPRB Draft Guidelines Consultation

The following comments are provided by Canadian PKU and Allied Disorders Inc. (CanPKU), a patient advocacy and support non-profit, in response to the Patented Medicine Prices Review Board Draft Guidelines Consultation 2019. The evidence we hereby submit speak powerfully for the need for sober second thought before the draft guidelines and indeed the new Regulations take effect.

CanPKU was a signatory to the Best Medicines Coalition (BMC) comments filed in response to the proposed regulatory changes that led to these proposed Guidelines. BMC called for a balanced and fair regulatory framework for pharmaceutical pricing aimed at sustaining the life, health and wellbeing of patients. BMC described the goal of a regime that that facilitates the introduction and availability of a comprehensive range of medicines, with the ability for patients to access necessary medicines in a timely manner.

The draft guidelines reflect the fact that the PMPRB Regulations, as published in August 2019, do not represent a balanced approach, and appear intended to manage public drug plan expenditures without regard to patient health outcomes and ration access to new therapies for unmet needs of patients rather than establish an economic framework to establish a non-excessive ceiling price. As such the Regulations and the draft guidelines are of questionable legality and ethics and are not providing due regard to improving patient health care outcomes.

CanPKU

CanPKU is a non-profit association of volunteers, first organized in 2008. We are dedicated to providing accurate news, information and support to families and professionals dealing with phenylketonuria and similar, rare, inherited metabolic disorders. Our mission is to improve the lives of people with PKU (phenylketonuria) and allied disorders and the lives of their families. By allied disorders, we mean other rare, inherited metabolic disorders also detected by newborn screening.

CanPKU has a membership of about 300 and represents 2,500 Canadians living with PKU plus their families.

CanPKU has adopted a Code of Conduct regarding funding that reflects a commitment to ensure that the important advocacy activities of CanPKU, pursued in support of its mission and goals, as well as the activities of its members, are not jeopardized by potential or perceived conflicts of interest, duty or loyalty related to funding arrangements or working relationships. This Code of Conduct is based on that of the Best Medicines Coalition, of which CanPKU is a member organization. It is also informed by the Canadian Consensus Framework for Ethical Collaboration developed by the Best Medicines Coalition, Health Charities Coalition of Canada, Canadian Medical Association, Canadian Nurses Association, Canadian Pharmacists Association and Innovative Medicines Canada.

PKU

PKU is a rare, genetic disorder of metabolism which threatens the human brain and affects approximately 1 of every 15,000 babies born in Canada. The current standard of care is that every baby borne in Canada - but not necessarily in the case of a child born abroad whose family later comes to Canada - has a blood sample taken on the second day of life and analyzed at a biochemical genetics laboratory in a tertiary care hospital.

PKU patients lack the normal functioning of the one enzyme in the liver (called phenylalanine hydroxalyze) needed to turn phenylalanine (phe), an amino acid in protein, into another amino acid, tyrosine. This results in an accumulation of phe in the blood which crosses into the brain where it is neurotoxic, causing various degrees of mental deficiency and neurological issues. Due to the scientific miracle of universal Newborn Screening Programs begun in the 1960s, described by the USA CDC as one of the top ten victories of public health in the 20th century, almost all patients in Canada are diagnosed and started on lifelong therapy within a couple weeks of birth and are able to avoid the more serious mental defects associated with untreated PKU. However, a late-diagnosis can mean that some brain damage occurs before the proper treatment was implemented.

PKU is treated first by a severe restriction in the intake of all forms of natural protein – at least 80%. In fact the degree of protein restriction is incompatible with life. Hence the need for PKU therapy.

For 99.999 % of the population, those without PKU, a small portion of the phe eaten each day is used for growth and for a process in every cell called protein synthesis and the leftover phe is

turned into Tyrosine. Tyrosine is used to make the neurotransmitters norepinephrine and epinephrine, which relay nervous system messages throughout the body. Since only a small portion of phe is used for body growth, and the remaining phe can't be broken down into Tyrosine, the medical therapy of a PKU patient needs to be calculated very precisely. PKU patients are at risk of both too much or too little phe and too little Tyrosine, so they can only eat the amount of phe needed for growth each day, but no more so that a buildup of phe in the body doesn't occur. Each PKU patient is prescribed an individualized target for phe intake; this target is both a maximum and a minimum, so the patient and family walk a tightrope each day to prevent brain damage. Blood-phe levels are monitored frequently by testing at the few biochemical genetics laboratories in tertiary care hospitals and the therapy is adjusted by specially trained doctors and clinical dietitians according to the results of the blood tests, any illnesses and/or behavioural changes. PKU therapy includes monitoring Tyrosine levels and when low, supplementing Tyrosine. The dangers of PKU medical diet therapy are neurotoxicity from too much phe or growth limitations from too little phe and low levels of neurotransmitters if not enough Tyrosine.

PKU Treatment – The Need for better therapies for better outcomes

The original way to treat PKU was to eat a special, highly restrictive medical diet under medical supervision that strictly limits foods containing phenylalanine. It also includes consuming several times a day a special prescribed medical formula with zero phe that provides the essential amino acid Tyrosine and other amino acids. Medical PKU formulas and foods are funded by all federal, provincial and territorial governments/government drug plans – with the exception of medical foods not yet funded by the province of Newfoundland and Labrador. While the medical formulas and foods are regulated by Health Canada for restricted access, they are not issued Drug Information Numbers and as such are outside the jurisdiction of PMPRB.

Individuals need to rigorously track and record <u>everything</u> that is ever eaten or drunk. This is essential for both the meal-to-meal, day to day management of the disorder, and as a reference to determine what has caused a high or low blood-phe level or a low Tyrosine level. For PKU children, this task falls to parents, and includes tracking what is and is not eaten at home, daycare, school, or when visiting family, neighbours or friends.

Despite being treated early and continuously with medical diet alone, children and adults with PKU may experience cognitive symptoms, as well as disturbances in emotional and behavioural functioning – including executive function deficits, attention deficits and reduced processing speed. It is common for early diagnoses and well-treated PKU children to start having problems in school around Grade Four.

Further, adherence to the lifelong medical food-based low-phe diet in PKU is extremely challenging. The planning required to achieve acceptable blood phe levels is very complex and time consuming, and the food is limited, expensive and unpalatable, especially the medical formulas. Published data is that +75% of older children, teenagers and young adults are unable to maintain the treatment with results in therapeutic range. In other words the original standard of care produces undesirable, suboptimum outcomes. Hence there is an unmet need for better therapies. Our goal is for breakthrough therapies which provide for normal levels of phe on a

normal diet resulting in normal brain function. This goal cannot be achieved today with existing, approved therapies.

One drug has been approved in Canada for the treatment of PKU. Health Canada approved sapropterin dihydrochloride (Kuvan) for PKU ten years ago, in 2010, as the first new treatment for PKU in 60 years. The saga of Kuvan after Health Canada approval is testament to the inability of the government drug "system" to adequately address the needs of Canadians with rare disorders.

The Kuvan Ten-Year Saga

– how governments continue to fail to deliver a better therapy to patients with unmet needs

The problems associated with ensuring adequate and appropriate access to Kuvan under Canada's public drug plans is not a result of problem with the PMPRB ceiling price, as it was. In fact, under the old rules PMPRB considered Kuvan to be a breakthrough therapy. It was the rest of the government drug system which has failed and continues to fail PKU patients.

There was/is a managed access agreement from 2013, though, and the criteria have been found to be extremely restrictive and not evidence based, and no patient has yet to meet these demands, except one or two in Ontario. Physicians who treat PKU have criticized in writing in public on multiple occasions the existing criteria as lacking clinical sense and for being developed without relevant expert consultation. CADTH, after its fourth consideration (Submission, reconsideration, request for advice and second submission) of this drug, recommended workable clinical criteria in October 2016. However to date – 3.5 years later - not even one government drug plan has implemented the workable criteria. This is both outrageous and shameful. Perhaps in total a case of government bureaucrats saving money by in effect practicing medicine, contrary to our criminal law.

Based on this unfinished Kuvan saga, we submit there is a reasonable basis to fear the draft guidelines under the 2019 PMPRB Regulations will make things worse for patients including PKU patients. The USA Food & Drug Administration in 2018 and the European Medicines Agency in 2019 approved the second drug for PKU. When, if ever, will it be available in Canada?

After a decade on the market for the first PKU drug – sustained by consistent coverage by private drug insurance in Canada and a generous compassionate access program funded by the drug developer– there is still no evidence for PKUers of a Canadian drug system that facilitates the introduction and availability of a comprehensive range of necessary medicines in a timely manner.

The new Regulations, and these proposed Guidelines, have been specifically shaped to reflect how the "the perspective of the public health care system". The public health care system has demonstrated its ability to avoid an appropriate access solution for more than 10 years for those PKU patients who need the clinical benefits of the first drug to treat PKU. It beggars belief that - under the proposed Guidelines as falsely claimed by some in government - Canada will continue to represent a market that that facilitates the introduction and availability of a comprehensive range of medicines. CanPKU submits that the evidence of misperformance and indeed

misconduct of government drug programs and their officials regarding Kuvan over a period of ten years is a very bad sign for what will happen to other newer treatments for PKU approved and funded elsewhere or under development – such as curative cell and gene therapies. The evidence of the Kuvan saga strongly indicates that these new therapies will not be available in Canada in a timely fashion, if ever.

Please colour us skeptical about the credibility gap between the words of the Government of Canada regarding changes in price controls through PMPRB regulations versus the real-world evidence we have cited here of actual impacts on patients.

Specific Comments on the Proposed Guidelines

Gender Based plus Analysis – Needed but lacking – the Burden on mothers as caregivers

Gender-Based Analysis Plus (GBA+) is the name for a process by which a law, regulation, policy, program, initiative or service can be examined for its impacts on various groups of women and men. GBA+ provides a snapshot that captures the realities of women and men affected by a particular issue at a specific time. This means that analysts, researchers, evaluators and decision makers are able to continually improve their work and attain better results for Canadian men and women by being more responsive to their specific needs and circumstances.

Treasury Board of Canada policy requires[1] federal departments and agencies to determine whether there is a potential gender issue within the proposed policy, program, initiative or service. Should such a potential exist, the policy expects the organization to fulfill its commitment to undertake a thorough and complete GBA+ assessment. The entirety of Health Canada's gender analysis for the Regulations[2] was restricted to examining the proportion of prescriptions received by males and females. We submit that approach was too narrow, profoundly unfair and perverse in its implications and results.

One of the key underlying reasons for making the changes to the Regulations, and these proposed Guidelines, was the need to address the problem of high-cost drugs, and in particular, those drugs for rare diseases. It is clear that the impact and burden of a rare disease differentially affects the genders. Most rare diseases present themselves in childhood – PKU presents at birth - and roughly 2/3 of Canadians with a rare disease are children. Even with increased newborn screening, in most cases it takes on average 4.8 years to receive an accurate diagnosis of a rare disease.

There is ample research and evidence demonstrating the financial, emotional and physical burden that faced by parents and caregivers of children with complex medical needs. As described above, management of PKU requires constant vigilance and attention over your child's dietary intake of protein in everything drunk or eaten. The need for this vigilance is unrelenting and also carries the reminder that a mistake or omission could result in harms to your child's cognition, including executive function deficits, attention deficits and reduced processing speed.

[1] https://www.canada.ca/en/treasury-board-secretariat/services/treasury-board-submissions/gender-based-analysis-plus.html
[2] http://canadagazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html

This caregiver burden falls predominantly on mothers. In a recent Canadian Organization of Rare Disorders survey of caregivers, 86% of respondents were female.

Despite false claims[3] that the Guidelines reflect a "commitment to support Canadians with rare diseases", the proposed Guidelines will substantially constrain drug prices.

It can be said that the previous PMPRB regime was price controls "light." What is now debatable is whether the new regime of regulations and guidelines will be price controls "medium" or "heavy". It is fair comment that the heavier the actual price controls become, the worse the impacts will be on patients with unmet needs, including PKU patients, in terms of access to new and better medicines.

These constraints by the federal government are highly likely to affect the attractiveness of the Canadian market for the introduction of new medicines, and specifically drugs for rare diseases, including PKU.

It is incumbent on PMPRB and Health Canada – indeed Treasury Board and the whole of Government - to establish that these Regulations and Guidelines, do not have a disproportionate negative impact on women and mothers. So far, this analysis has not been undertaken or complete. This failure conflicts with Government policy and needs to be remedied.

Draft Guidelines/Regulations Claim to be Risk-based: True or False?

Risk-based approaches to regulatory design and compliance are employed for a variety of reasons. Principally, it allows a regulator to deploy scarce resources where they are of most use or benefit. This should maximize effectiveness of regulations by emphasizing effort where the risk of harm is greatest. This approach also recognizes the costs of regulation and reduces the burden of regulation where risk of harm is lowest.

Risk-based regulation should be a responsive or dynamic process that includes explicit risk assessments, targeted risk management techniques, and clear and transparent risk communication. Health Canada and PMPRB have frequently described the Regulations and the proposed Guidelines as risk based, but there is little evidence to support the claim.

First, the use and application of the updated schedule of comparator countries applies indiscriminately to all patented medicines under regulation. That approach is not based on risk.

Second, nothing in the draft Guidelines addresses or considers price constraints that exist outside of the PMPRB framework, or the presence of competition that could be used to prevent excessive pricing without regulatory constraint. There are a substantial number of patented medicines under PMPRB jurisdiction that face multiple in-class competitors, as well as many products that have lost market exclusivity and face competition from generics. A risk based approach would limit regulatory intervention in these cases.

[3] https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html

Finally, the criteria for "Category 1" drugs don't seem to do anything other than capture drugs that cost public drug plans a lot of money.

General

A plain language, outsider reading of the draft Guidelines does not substantiate the idea that the intent is "to identify a national ceiling price above which it would be unreasonable for any consumer in Canada to pay[4]". These draft Guidelines do not seem designed to prevent excessive pricing – they appear designed instead to manage the expenditures of public drug plans or to establish a "reasonable" or "affordable" price. This notion is reinforced by the fact that Health Canada specifically stated that "the policy intent is for the PMPRB to adopt the perspective of the public health care system and favour a supply-side cost-effectiveness threshold in estimating opportunity cost.[5]" If the Canadian market for patented medicines is to include multiple consumers or purchasers, then it is unreasonable to superimpose the perspective of the "public health system" onto "any consumer". These two concepts can't coexist in a rational way.

Public Health Care System Perspective – A danger for patients based on Kuvan saga

PMPRB have presented the draft Guidelines, as fulfilling a Government of Canada "policy intent" of adopting "the perspective of the Canadian public health care system" in their "role as a ceiling price regulator, not a price setter". A review of the various government consultation documents that have led to the Guidelines fails to identify this policy intent, and the question of the appropriate "perspective" has not been examined in a public way.

The Health Canada whitepaper *Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations*[6] does not identify a specific policy intent or objective from the proposed regulatory changes. Nowhere in the Whitepaper is there a discussion of what or whose perspective should be adopted when regulating ceiling prices for patented medicines. The Whitepaper does suggest that the regulatory changes considered would require the Board to consider whether a medicine's price is commensurate with the benefits it provides to patients **within the context of the Canadian health care system** (emphasis added). Of course, the Canadian health care system has multiple markets, multiple payers, and a system with individual autonomy.

Similarly, the proposed modifications to the Patented Medicines Regulations, and the accompanying Regulatory Impact Assessment Statement[7] (RIAS) does not contain any clear statement about policy intent or policy objectives. Again, the RIAS suggests the HTA factor would determine whether a medicine's price is commensurate with the benefits it provides to patients **within the context of** the Canadian health care system (emphasis added). The Canadian health care system is complex, it has multiple payers, and it includes the perspectives of many actors: public administrators; private insurance actuaries; employers; and most importantly,

[4] http://canadagazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html
[5] http://canadagazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html
[6] https://www.canada.ca/en/health-canada/programs/consultation-regulations-patented-medicine/document.html
[7] http://gazette.gc.ca/rp-pr/p1/2017/2017-12-02/html/reg2-eng.html

individual Canadians and their caregivers. There is a substantial and material difference between "within the context of" and "adopt the perspective of".

The first public evidence CanPKU can find of this stated "policy intent" is in Minutes[8] to a meeting of the PMPRB's Technical Working Group discussing the Guidelines. Members of the group were asked to provide opinions and consideration of possible perspectives (public health care system vs societal) during the meeting. According to the Minutes, towards the end of the discussion/meeting, Board Staff apparently confirmed that the policy intent was to adopt the healthcare system perspective. It's hard to assess the validity of a "policy intent" that has not been subject to any public scrutiny, and was dictated to even the technical experts tasked with providing advice about the Guidelines.

Only once the Regulations were published[9] in final form was any policy intent or objective clearly articulated by Health Canada. It was only in that document that the Government of Canada stated a policy intent or a policy objective for any changes to the Regulations. The publication of the final Regulations was the first time the Government of Canada made it clear that intended for PMPRB to adopt the perspective of the public health care system.

Finally, from the experience with trying to get access and public coverage of the first PKU drug, Kuvan, it is quite evident that the perspective of the public health care system does not fully align with the health and wellbeing interests of individual citizens.

The debate about "appropriate" drug coverage is not a balanced one. Average Canadians have modest needs from their drug plans (private or public), but they expect that if a treatment was ever needed it would be available to them. When there is a need for a treatment, and there is no coverage, it's too late for debate. The outcome of late discovery of lack of coverage is harm to patient health. Those harms are real and the hidden subsidy patients are forced to make involuntarily to subsidize budgets. CanPKU submits that despite representations otherwise from PMPRB, the question of what the appropriate perspective that should be applied is an open, unresolved, and untested question – and should be subject to rigorous public discussion.

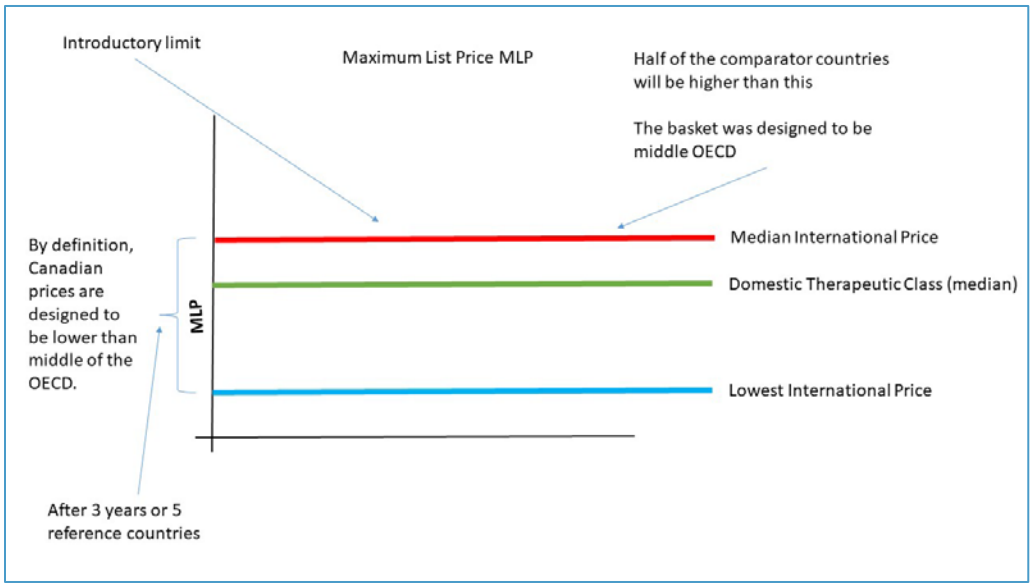
New Factors in Regulations/Guidelines

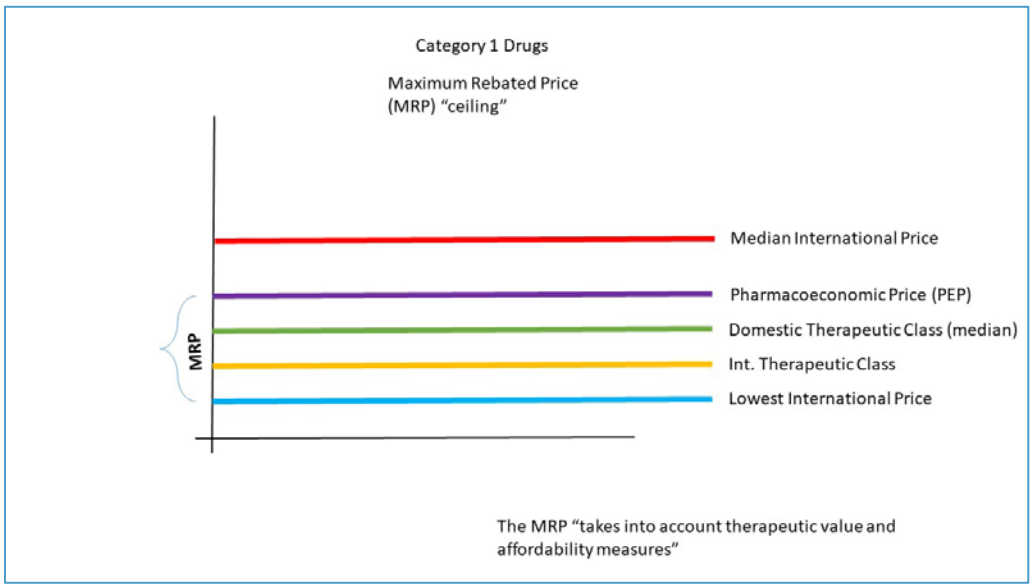
The application of the new additional factors is duplicative and redundant, hence a waste of taxpayer resources. The basket of comparator countries was amended to include countries that "constrain free market pricing for medicines" through policy measures. Therefore, application of the new basket of comparators AND additional factors applies price constraints at least twice. Neither Health Canada nor PMPRB have addressed this issue, or provided a rationale for doubling up on price constraints.

The way the draft Guidelines apply the list of comparator countries further demonstrates that this is not an exercise in establishing a non-excessive price ceiling. The list of comparator countries was established to reflect "median OECD prices[10]". If this is the case, with the manner the

[8] http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1443&lang=en
[9] http://gazette.gc.ca/rp-pr/p2/2019/2019-08-21/html/sor-dors298-eng.html
[10] https://www.canada.ca/en/health-canada/programs/consultation-regulations-patented-medicine/document.html

comparator list is applied, the OECD median becomes more or less the ceiling. It is hard to reconcile the goal of Canada being a market that facilitates and encourages the introduction and availability of a comprehensive range of medicines - including novel treatments – in a timely fashion, when a manufacturer cannot seek a list price above the middle of price levels in OECD countries.

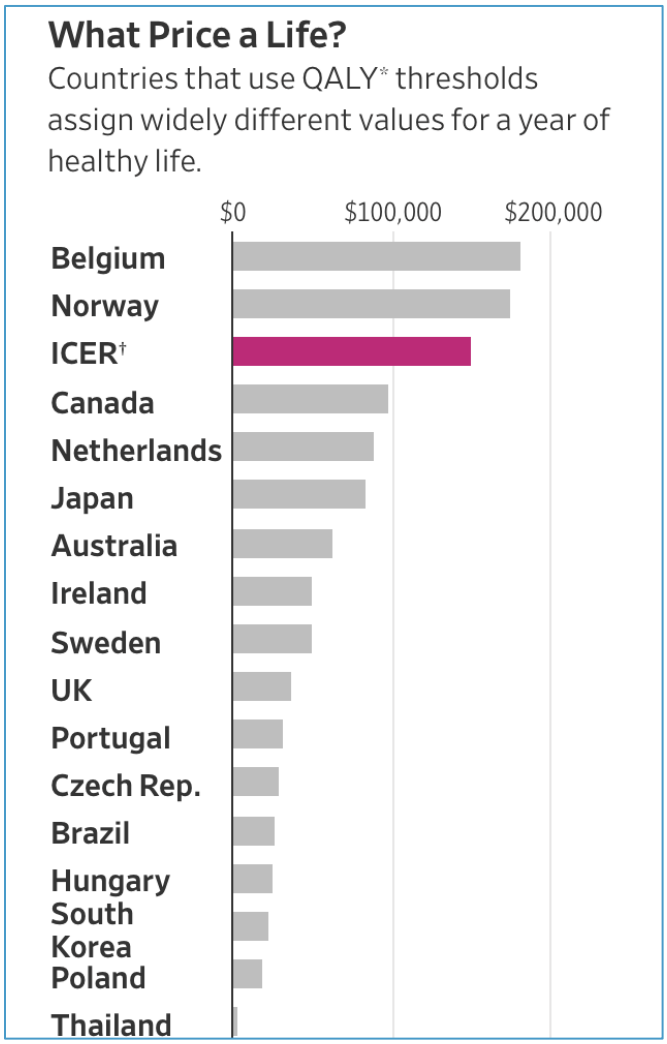




As noted, use of international benchmarking already accounts for the use of price constraints in those other countries. Use of the Median International Price as the absolute ceiling price in Canada says that no Canadian consumer or payor could ever reasonably pay a price that is acceptable (and subject to price constraints) in half of the comparator countries.

It is quite telling that the Guidelines describe a "price floor[11]" set by the lowest international price. This is certainly not a price floor as normally understood by economists – a regulated lower limit for the price that might be charged for a product. This "floor" is in fact a lower limit on the "ceiling" price that the PMPRB Guidelines might set. Clearly PMPRB anticipates that the Guidelines as constructed could result in a mandated non-excessive ceiling price lower than the acceptable price in any of the other comparator countries. The Guidelines seem to offer this "floor" as a concession. Even so, it means that for some patented medicines, the Canadian ceiling price is the lowest of all acceptable prices in all of the comparator countries. This is inconsistent with the idea that PMPRB establishes non-excessive price ceilings, and is not attempting to set prices. It is also inconsistent with the idea that Canada will continue to be a market that encourages early introduction of new medicines.

HTA Factor



Health Technology Assessment (HTA) can be a useful tool to provide guidance to decision makers. At the same time, there is a long list of well-known problems and limitations for ICERs (Incremental Cost Effectiveness Ratio) and QALYs (Quality Adjusted Life Year). . The Regulations and the proposed Guidelines ignore commonly accepted limitations of these tools and again reinforce the impression that they are intended to manage public drug plan expenditures rather than establish an economic framework to establish non-excessive ceiling prices.

Cost effectiveness thresholds are generally used to inform government decision making about the amount it should be willing to spend in adopting new medical technologies. There is no consensus on whether they should be used or how to establish a threshold. Countries that use QALY thresholds assign widely different values[12] . The use of opportunity costs includes the assumption that the health system budget is fixed with no ability to increase expenditures even when a scientific breakthrough can move a

[11] Paragraph 39, https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html
[12] https://www.wsj.com/articles/obscure-model-puts-a-price-on-good-healthand-drives-down-drug-costs-11572885123

devastating disease from untreatable to treatable, or in the new era of cell and gene therapies, to curable.

It is important to remember that cost–effectiveness ratios derived from economic modelling are simply estimates[13] –based on several assumptions – produced to indicate the potential value for money of one or more interventions. The construction of economic models is prone to problems and errors. These estimates and internal biases have significant influence on the outcomes on the determination of QALYs, or DALYs (Disability Adjusted Life Year), ICERs, or any other economic construct measuring value.

CanPKU rejects the notion that PMPRB ought to apply the perspective of the Canadian public health care system in setting non-excessive ceiling prices. PMPRB has confirmed the inherent uncertainty in ICER values and the cost utility analyses upon which they are based. It is not possible to reconcile this uncertainty by unilaterally applying a unitary perspective. The RIAS includes the following admonition - the PMPRB's approach to giving effect to this new factor must align with its role as a price regulator, not a price setter.

If the HTA factor is to be applied, it should not be narrowly established using only the perspective of the public health system, but the economic modelling should cover the range of assumptions and inputs that reflect the whole variety of Canadian patients, consumers, and payers.

Conclusions

CanPKU continues to call for a Canadian drug pricing regime that facilitates the rapid introduction and availability of a comprehensive range of medicines and that provides Canadians the ability to access necessary medicines in a timely manner. Current practice in Germany is evidence of a useful alternative. The draft Guidelines do not reflect such a regime or intent. It is hard to reconcile the idea of Canada being a market that facilitates the introduction and availability in a timely fashion of a comprehensive range of medicines - including novel treatments – when a manufacturer cannot seek a list price above the middle of price levels in OECD countries.

CanPKU believes it is important that Canada be a market where novel treatments for unmet or poorly met needs are brought to market rapidly. The fact that the proposed absolute ceiling price in Canada says that no Canadian consumer could ever reasonably pay a price that is acceptable in half of the comparator countries would suggest we can expect to have no better than middling availability of new medicines.

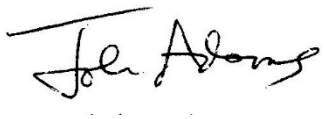
[13] https://www.who.int/bulletin/volumes/94/12/15-164418/en/#R15

CanPKU has identified the following specific deficiencies that PMPRB should address if we are to hope to achieve any sort of balance in this new pricing regime

- Address the Gender-based analysis and ensure the Guidelines and Regulations do not have a disproportionate negative impact on women and mothers.
- Apply a true risk-based approach to the guidelines and Regulations
- Engage in an open transparent public discussion about the appropriate "perspective" for the Guidelines and Regulations
- Economic modelling for the HTA should cover the range of assumptions and inputs that reflect the whole variety of Canadian patients, consumers, and payers.

PMPRB have made it clear that it believes that once applied, the Guidelines will result in prices that represent what the public health system is will to pay, is able to pay, and that reflect value for the Canadian Health system. Can PMPRB then assure Canadians that any drug sold at the regulated price will be covered by all public drug plans? Or will Canadians still have to wait, as Canadians with PKU have with Kuvan, for ten years or longer?

As the Supreme Court of Canada has stated in a medical care case, "Access delayed is access denied."



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August 4, 2020

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Re: PMPRB Draft Guidelines Consultation – Revised Guidelines of June 2020

The following comments are provided by Canadian PKU and Allied Disorders Inc. (CanPKU), a patient advocacy and support non-profit, in response to the Patented Medicine Prices Review Board Revised Draft Guidelines Consultation, as published June 19, 2020. The evidence we hereby submit reiterates the need for sober second thought before the draft guidelines and indeed the new Regulations take effect on January 1, 2021.

CanPKU was a signatory to the Best Medicines Coalition (BMC) comments filed in response to the proposed regulatory changes and the proposed Guidelines. BMC called for a balanced and fair regulatory framework for pharmaceutical pricing aimed at sustaining the life, health and wellbeing of patients. BMC described the goal of a regime that that facilitates the introduction and availability of a comprehensive range of medicines, with the ability for patients to access necessary medicines in a timely manner.

CanPKU filed comments in response to the draft Guidelines, supporting the BMC position and highlighting the fact that the draft Guidelines do not seem designed to prevent *excessive pricing* – but rather to manage the expenditures of public drug plans or to establish a "reasonable" or "affordable" price. Further, CanPKU raised a number of issues that have not been addressed, either in the revised Guidelines, or in the "Backgrounder" document. Specifically, CanPKU called on the PMPRB to address the following:

- The absence of a gender-based analysis, as required by federal policy, to ensure the Guidelines and Regulations do not have a disproportionate negative impact on women and mothers;
- The duplicative application of price constraints through the new list of reference countries plus the additional economic factors;
- The absence of a true risk-based approach to the guidelines and Regulations; and
- The inappropriate application of the "perspective" of the public health system for the Guidelines.

None of these issues have been acknowledged or addressed, and as a result, the problems they pose remain in the revised Guidelines. Nothing in the revised Guidelines changes the underlying problems with the Regulations, or the problems with the interpretation and application of the Regulations by PMPRB staff.

Under the revised Guidelines, the ultimate maximum regulated price for any patented medicine in Canada is effectively the OECD median, and everything else in the Guidelines pushes the "non-excessive" price below that. CanPKU provided substantive comments on the specific application of the new "factors" in our previous comments. The June revisions have made changes at the margin, but retain the intent and outcomes of the original Guidelines. As a result, CanPKU will not provide specific comments on the tweaks to the individual new factors. Our previous comments remain valid.

Balance of Interests?

CanPKU shares the BMC position that that Canada needs effective, balanced, and fair pharmaceutical pricing rules which contribute to sustaining and improving the health and wellbeing of current and future patients. Regulations and guidelines must achieve the following:

> ***Improved Affordability of Medicines.*** We support the goal of improving the affordability of medicines, both for individual patients, health care systems and private and public insurance. Patients and their families, and those who pay on their behalf, bear a significant burden of prescription drug costs, and we support the government's intention to address this, particularly in relation to appropriate international comparators.
>
> ***Comprehensive Access to Medicines.*** Of equal importance, patients need timely access to new drugs which meet unmet needs. There must be confidence, based on best available evidence, that policies, regulations and guidelines will facilitate and not discourage rapid introduction of a full range of medicines and vaccines and access to clinical trials sponsored by drug developers which provide willing patients early access to promising new therapies.
>
> ***Accountable, Transparent and Inclusive Governance.*** Canadians expect that public health care agencies adopt up-to-date governance which upholds and demonstrates transparency and accountability. Relevant stakeholders, including patients, must be included in policy setting and decision making. PMPRB has work to do to begin to approach best practices in this regard.

CanPKU continues to call for a Canadian drug pricing regime that facilitates the rapid introduction and availability of a comprehensive range of medicines and that provides Canadians the ability to access necessary medicines in a timely manner. The Canadian public health care system, unlike private insurance, has demonstrated its ability to avoid an appropriate solution for patient access more than 10 years for those PKU patients who need the clinical benefits of the first drug to treat PKU. It beggars belief that - under the proposed Guidelines as falsely claimed by some in government - Canada will continue to represent a market that that facilitates the introduction and availability of a comprehensive range of medicines. CanPKU submits that the evidence of misperformance and indeed misconduct of government drug programs and their officials regarding the drug Kuvan over a period of ten years is a very bad sign for what will happen to other newer treatments for PKU approved and funded elsewhere or under development – such as curative cell and gene therapies. The evidence of the Kuvan saga among the government drug programs strongly indicates that these new therapies will not be available in Canada in a timely fashion, if ever.

It is hard to reconcile the idea of Canada being a market that facilitates the introduction and availability in a timely fashion of a comprehensive range of medicines - including new treatments – when a manufacturer cannot seek a list price above the middle of price levels in OECD countries. We believe the "backgrounder" document is the first time that anyone in the government of Canada has explicitly stated this as a policy goal. Here is that statement:

> *As a general rule, the Board feels that Canadian list prices higher than international norms smacks of excessiveness and the MIP is an appropriate litmus test for ensuring that Canadian list prices do not become excessive in the future*[1]

This objective has been implicit throughout the process since the PMPRB *Guidelines Modernization* discussion paper. The problem is that government officials have been fastidious about avoiding any frank and clear statements of intent or goals for the regulatory changes. It is difficult to have a transparent and fruitful public discussion when the vision for changes are withheld from public understanding or scrutiny. In any event, it is clear that this goal could and would be accomplished simply by using price referencing with the new list of countries.

CanPKU calls on the PMPRB and the Government of Canada to make public and explicit what are the goal(s) for drug price reductions.

Evidentiary Basis for Policy Decisions

On the topic of transparency and openness in the development of the Regulations and Guidelines, we note that unlike any other Canadian regulator, PMPRB staff produce, develop and editorialize the data and statistics underpinning policy decisions. Policy making and data collection/reporting are normal and legitimate activities of a regulator. Canadians should expect that those activities are separated in a way that ensures data informs decision making, rather than decisions informing data selection. Unusually, there is a palpable linkage between PMPRB policy development and the way that data is collected and presented.

[1] PMPRB Backgrounder on June 2020 Guidelines, p.7

We will highlight the fact that PMPRB held 3 "research" webinars during the consultation period for revised Guidelines. These webinars covered 6 different topics about "analyses expected to inform the consultation". PMPRB staff presented data in 89 mostly new charts. The last webinar was scheduled 4 days before the original comment deadline. The timing for these webinars and the data presented was not conducive to meaningful review and comment. Frankly, the content and conclusions of the presentations were clearly prepared to support and reinforce existing PMPRB staff positions and proposals. As a participant in the Regulation and Guidelines development process, and attendees at the webinars, our observation is that these webinars did not represent an impartial presentation of all relevant facts associated at issue in this consultation about public policy.

Phased implementation

As we observed in previous comments, the application of the new additional factors is duplicative and redundant. The basket of comparator countries was amended to include countries that "constrain free market pricing for medicines" through policy measures, i.e. price controls. Therefore, application of the new basket of comparators AND additional factors applies price constraints at least twice. Neither Health Canada nor PMPRB have addressed this issue, or provided a rationale for doubling down on price constraints.

If the goal is to reduce drug prices to below the OECD median, then how far below that benchmark? The comments of PMPRB and the Government of Canada so far have been unclear in this regard.

BMC has taken the position that these regulations and guidelines introduce too many measures at the same time, and some of these measures can be considered experimental having never been tried elsewhere or within the unique Canadian system. Consequently, BMC proposed phasing in aspects of the regulations and guidelines to meet the goal of increasing affordability without additional measures which may have unintended negative impact on patient access to new medications. Specifically, BMC has suggested the application only of the revised basket of comparator companies, and moving the economic factors to a second phase, if necessary.

Modifications to Proposed Guidelines

Improvements

A few of the modifications made to the Guidelines in the latest draft do present some improvements that seem designed to minimize the impact of price reductions on existing medicines, including the use of Highest International Price based on the PMPRB11 basket of comparator countries, as well as the application of the new economic factors only to new medicines. These existing products were brought to Canada under the previous regime, and for public access, faced HTA reviews by CADTH and/or INESSS, and negotiated listing agreements. It should be fair to say that those product agreements reflect the willingness and ability to pay of the public drug plans. Further, the changes to the criteria for "Category 1" drugs have been revised to reduce the number of drug subject to the additional tests. We objected to the absence of meaningful risk assessment. We commented that the criteria for "Category 1" drugs didn't "seem to do anything other than capture drugs that cost public drug plans a lot of money".

These changes are improvements because they reduce the number of products subject to the test, but the changes do not address the underlying problems with the approach. Drugs for rare diseases (like PKU) remain as principal targets for price constraints. The greatest risk from our perspective remains that overly restrictive price constraints will delay or prevent new medicines from being launched in Canada and thus harm the health of patients going without these therapies.

Concerns

We do have concerns with specific elements of the revisions to the proposed Guidelines. These concerns are generally in areas where we believe the changes have increased the level of arbitrariness, complexity, or uncertainty.

We understand that Guidelines cannot be binding on staff or the Board, but the language that permits staff to "utilize any of the tests described in the Guidelines and modifications or variations of those tests" during an investigation seems to be arbitrary. It would seem reasonable that – in the absence of a clear and compelling rationale, the same standards would apply at introduction and during an investigation. Anything less can be seen as a deviation from the fundamental principles of natural justice.

The application of elements of the Therapeutic Criteria Level (TCL) are particularly confusing. Patient groups made it clear that the therapeutic benefit of a new medicine should be taken into account in value deliberations. In our view, this is one process that should certainly include input from Canadians, something the PMPRB has not done well in the past. The proposal to allow staff to determine the relevant indication should be revisited. A cynic might guess that the Guidelines proposal in paragraph 69 for selecting the relevant indication was selected simply to maximize price constraints. From our perspective, the indication with the greatest therapeutic benefit should be considered relevant. In the absence of useful examples or case studies, it is difficult to determine the utility of this process for patients.

Conclusions

Despite the changes to the draft Guidelines, none of our key issues have been acknowledged or addressed. Nothing in the revised Guidelines changes the underlying problems with the Regulations and resulting Guidelines, or the problems with the interpretation and application of the Regulations and Guidelines by PMPRB staff.

These are generational changes that are being applied in a cavalier fashion. The patient communities, including CanPKU, have identified the risks we perceive from the changes. Even with the recent "research" webinars, we do not believe PMPRB or Health Canada have paid sufficient attention to those risks. The new Regulations and Guidelines together mean:

1. Increased uncertainties and threat of low prices will continue to lead to delays in launching in Canada new drugs or decisions not to launch

    This is already already happening in PKU. There has been a failure of the public health system to adopt and fund the initial approved therapy without taking more than ten years. The second and third generations of treatment may avoid Canada altogether.

2. Reduction in clinical trials sponsored by drug developers, and consequently fewer patients gaining early access to promising therapies through clinical trials

3. Combined with provincial coverage policies, patient support programs are jeopardized for specialty and rare disease drugs including for PKU patients, such as:

    - Specialty pharmacy services
    - Infusion services (when drug is infused)
    - Nurse and/or clinical dietician support and patient self-care training
    - Reimbursement navigation including for private payors
    - Co-pay assistance for drug and / or delivery devices (i.e. needles), and
    - Compassionate access for patients with little or no drug insurance (public or private)

These effects will be felt by patients and the health system over the course of years, not months or quarters. Recent evidence, and surveys of business sentiment provide signals of intent, but the real effect will happen over time. If the risks associated with the Regulations and Guidelines do manifest themselves, they will be profound, and will take a concerted effort to change and an equal time to correct. Much like the proverbial frog in a pot, Canadian grassroots patients and policy makers will not perceive the changes happening around them until it is too late.

CanPKU reiterates our comments and recommendations from February 2020 and support the conclusions of BMC. We will offer a few last recommendations for how the Regulatory and Guideline changes can best benefit Canadians and Canadian patients, as follows:

Recommendations:

1. The Government of Canada should make a public and explicit statement of its goal(s) for drug price reductions,

2. The Government and PMPRB should phased in the application of the regulations and guidelines to better manage risks of negative impact of these generational changes, starting with only the change in comparison countries.

3. The Government and PMPRB should commit and undertake comprehensive monitoring and evaluation of core metrics, specifically

    - drug launches (number and timing);
    - clinical trials (drugs and patient enrollment); and
    - patient access (time to listing, and provincial variances).

4. The Government and PMPRB should commit to and undertake meaningful processes for patient engagement and participation in decisions.

CanPKU believes it is important that Canada be a market where new treatments for unmet or poorly met needs are brought to market rapidly. We vigorously call for a Canadian drug pricing regime that facilitates the rapid introduction and availability of a comprehensive range of medicines and that provides Canadians the ability to access necessary medicines in a timely manner. Unfortunately, it appears policy makers believe a "last is best, and least risk" is most appropriate for Canada.

PMPRB and Health Canada have repeatedly said that once applied, the Guidelines will result in prices that represent what the public health system is will to pay, is able to pay, and that reflect value for the Canadian Health system. Canadian patient groups like CanPKU don't believe it, and this is a terrible game of chicken.

We will conclude these comments with the same (unanswered) question we posed in February, 2020. Can PMPRB assure Canadians that any drug sold at the regulated price under these new Regulations and Guidelines will be covered by all public drug plans? Or will Canadians still have to wait, as Canadians with PKU have with Kuvan, for more than ten years and counting?

Thank you for your consideration of this submission.

John Adams

Co-Founder, President & CEO

Canadian PKU and Allied Disorders