



# Response to Regulations Amending the Patented Medicines Regulations

Submitted by:  
Canadian Organization for Rare Disorders (CORD)  
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## **Preface: First Thoughts**

The Canadian Organization for Rare Disorders (CORD) welcomes the opportunity to provide input into the consultation on proposed amendments to the Patented Medicines Regulations (PMPRB Amendments) posted December 2017. However, for the record, we remain extremely disheartened that our comments submitted for the June 2017 consultation on the proposed regulatory changes were not recognizable in the summary of feedback from patient organizations nor were our concerns and recommendations reflected in the December 2017 proposed amendments.

That being said, CORD agrees wholeheartedly that the current patented medicines review process, from Health Canada regulatory review to the Patented Medicines Prices Review Board (PMPRB) through the panCanadian Pharmaceutical Alliance (pCPA) and into the (private and public) drug plans, is in need of review and reform. From the government's perspective, the proposed Amendments are considered necessary to redress the failures of the current regulations, which were designed to allow the PMPRB meet its goals of assuring "reasonable" drug prices and 10% pharmaceutical research investment. From our patient and public perspective, reforms are urgently needed to redress the failure of the Canadian drug assessment process to assuring that Canadians have timely access to the best medicines at the best prices for their individual need and societal benefit.

This deficiency in timely, appropriate and reasonably priced prescription drug access is accentuated with respect to Canadians living with rare diseases. Under current regulatory processes, especially in the absence of Canadian Orphan Drug Regulations, only about half of all orphan drugs approved in the United States or in Europe are available in Canada<sup>1</sup> and often not launched until years later. Moreover, only about one-fourth of the orphan drugs approved by Health Canada are funded through public drug plans with significant discrepancies across the provinces and territories.<sup>2</sup> Today, nearly 35 years after the passage of the Orphan Drug Act in the United States and 18 years following similar legislation in the European Union, Canada stands alone as the only "high income" country and one of the very few countries in the Organisation for Economic Co-operation and Development (OECD) without some form of orphan drug or rare disease legislation.<sup>3</sup>

## **Lacking: Patient Centred Principled Approach**

The proposed amendments to the Patented Medicines Act are presented devoid of the broader context of a Canadian pharmaceutical policy and indeed without commitment to the essential role of pharmaceuticals within the healthcare system. It has been a decade (and more) since two major reviews of Canadian healthcare, the Commission on the Future of Healthcare in Canada: The Romanow Commission<sup>4</sup> and the Michael Kirby Senate report<sup>5</sup>, both concluded that pharmaceuticals, specifically prescription drugs, are essential healthcare services and should be

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guaranteed in the Canada Health Act. Without this explicit commitment, a singularly focused agenda to reform (reduce) drug prices, like the proposed PMPRB Amendments, will inevitably result in poorer patient access to medicines, poorer patient outcomes, and poorer societal benefits. Prior to making regulatory reforms to a pricing mechanism, it is paramount that Canada engages in a comprehensive, multi-stakeholder consultation to articulate Canada's pharmaceutical policy. CORD offers, as starting points to the dialogue, the following three fundamental propositions or principles.

*Principle 1.* Medicines are essential healthcare and patients have right to timely access to the most appropriate safe and quality medicines for their individual needs

*Principle 2.* Pharmaceutical prices and drug budgets exist in a dynamic ecosystem, whereby prices are based on (predicted, demonstrated or most likely) therapeutic outcomes (relative to other treatment options) but are adjusted in the face of new (real-world) evidence of performance and impact; at the same time, drug budgets must be forecast to sufficiently accommodate old and emerging therapies with mechanisms to support cost-effective use and meet societal values (for example, equitable access, fair innings, and/or rule of rescue).

*Principle 3.* Canada must commit to participating as a top-tier country in innovative therapeutic research and development, and to that end, it should strive for a combination of volume and pricing for a pharmaceutical product that will generate sufficient (financial) incentives to the company to provide on-going support for appropriate clinical use and research for outcomes monitoring as well as incentives for future R&D in Canada.

### **Needed: Patient Centred Principles for Rare Disease Drugs**

CORD additionally proposes an articulated policy specific to drugs for rare diseases (DRDs) that recognizes the unique nature of rare diseases and is compatible with policies and procedures in other (OECD) countries.

*Rare Disease Principle 1:* Patients with rare diseases are entitled to equity in access to health services, which may entail inequity in the assessment of value of therapies.

*Rare Disease Principle 2:* Fair access should take into consideration societal preference (added value) for treatments for patients with severe and debilitating conditions where there are no good alternatives.

*Rare Disease Principle 3:* Regulatory approval of rare disease drug must take into consideration unique clinical trials designed to accommodate patient with rare diseases. For example, CTs that are defined by:

- Small patient numbers that preclude statistical analyses designed for large RCTs with unique phase 2 and phase 3 patient participants;
- Variability of disease and lack of natural history, which challenges well-defined patient outcome measures;

- Severity of conditions and lack of alternative therapies, which may preclude comparison with standard of care and also access to treatment on ethical grounds prior to conclusion of trial.

### **Essential: Investment in Innovation**

It is distressing that neither the Regulatory Impact Analysis Statement (RIAS) nor the PMPRB Guidelines Scoping Paper addresses the causes for lack of investment in research and development (R&D) in Canada. Notwithstanding the wide discrepancy between the PMPRB's calculated industry investment of R&D at 4.45% (of total sales revenues) and EY analysis of 9.97%,<sup>6</sup> there is an acknowledged need to cultivate a climate that is more competitive and inducing to pharmaceutical investment in Canada. Indeed CORD is very mindful of the strong warning issued by BIOTECCanada and co-signed by the provincial biotechnology organizations that the proposed amendments will “negatively impact the whole Canadian biotech ecosystem.”

With respect to investment in rare disease pharmaceutical research, CORD knows first hand and through feedback from our many patient communities that Canada is not perceived as a desirable environment for rare disease drug research and development. Compared to other countries, Canada lacks incentives, infrastructure, and policies supportive of exploratory academic/clinical investigation, early stage clinical trials, and early market launch. Compared to those in other countries, Canadian academic researchers have access to less start-up funding for rare diseases; similarly Canadians who discover promising therapies for rare diseases will move them to the United States or Europe where they can get orphan drug designation and access to capital investments. Canada's reputation as a “good place” to do clinical trials<sup>7</sup> does not generally extend to trials for rare disease therapies where infrastructure support and potential market access are limited.

### **Regulatory Goal: Equipping PMPRB as Effective “Price Monitor”**

Given the PMPRB's self-declared failure to meet its objectives of assuring “reasonable drug prices” and “sufficient pharmaceutical investment”, it is timely to consider a more substantive overhaul of the entity within the context of the overall (current) pharmaceutical system including Health Canada's revised regulatory approach (R2D2), revised CADTH functions and timelines (early submission, stream-lined reviews, new recommendation options), pCPA's enhanced scope of work (but increasing backlog) and changes to public drug plans. As a starting point, we ask whether the proposed Amendments address the fundamental reasons why the PMPRB has failed to fulfill its role as a “price setting” and “price monitoring” agency. Will changing the basket of countries really reduce the overall Canadian investment in pharmaceuticals?



More importantly, will the PMPRB's focus on driving "average" Canadian prices to a 12-reference country median create unintended harms, especially to patient access and research investment? For example, some analysts have pointed out that Canada's "higher than OECD median" drug prices are correlated with "earlier launches" of new drugs in Canada. From a patient perspective, that is a very desirable outcome.<sup>8,9</sup> Moreover, despite the calculations provided in the scoping document, we are not confident that the additional reporting and monitoring requirements will really be (much more) effective given the lack of transparency and possible validation of actual domestic and international prices. We are not aware of any other country that is adopting this strategy and it can only serve to disenfranchise manufacturers.

As importantly, CORD is concerned that the PMPRB, in redefining its process is also redefining its mandate, from monitoring potentially "excessive" prices to addressing "budget affordability" without clearly specifying whose budget it is defending: public drug plans, private insurers, and/or individual payers. Clearly, excessive pricing and budget affordability are very different concepts, whereby monitoring "excessiveness" is clearly aligned with PMPRB's legislated mandate but evaluating "affordability", not really. Moreover, we contend that "affordability" is not solely an economic concept but a political and social one, anchored in spending priorities and budget allocations, so affordability cannot be measured with economic factors alone. In contrast, determining whether a price is "excessive" requires comparison to a benchmark with determinants that are not only objective (cost, profit, return-on-investment) and but also subjective (equal, equitable, outcomes-based, early adopter). So even the determination of excessiveness requires consideration of factors that are beyond the economics. Overall, we are unsure whether PMPRB's revised procedures can improve their capabilities to assure "non-excessive" prices; however, we are *very* sure that PMPROB is not appropriately positioned, structured, or resourced to address "affordability" of new therapies.

An equally troubling question that patients have regarding the PMPRB's revised process is whether the PMPRB could and should use pharmacoeconomics (PE) to set a legally binding ceiling price that is based on a standard "cost per QALY." Indeed not all of the other countries in the 12-country reference basket rely on a targeted "cost per QALY" and none establish a PE-based ceiling price prior to market entry. We are not aware of the actual process that PMPRB will be using to arrive at a value-based priced, but we have been informed that the economic evaluation will be conducted by CADTH. Under the current CADTH process, company-submitted PE analyses and CADTH-conducted PE analyses often yield widely discrepant outcomes, presented as incremental cost-effectiveness ratios (ICER's) or cost per quality-adjusted life year (\$/QALY). These differences are especially pronounced for innovative and rare disease drugs where their input and output measures as well as other factors may be highly uncertain. As a result, CADTH often recommends a price reduction (never an increase) to improve cost-effectiveness (sometimes a specified amount).

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What is different from the proposed process is that the CADTH recommendation is used as a starting point for negotiation and does not constitute a ceiling (non-excessive) price. There are many other elements that can be brought into the negotiation to improve cost-effectiveness and/or reduce risk to the payer, including risk-sharing agreements, managed access plans, patient-support programs, patient screening and registries, and post-market monitoring. The Canadian negotiation process parallels the type of negotiations undertaken between industry and payer in other countries. Under the proposed PMPRB amendments, companies could decide not to bring a product in Canada or they will wait to launch until prices have been established elsewhere. These outcomes, which are highly likely, would be extremely detrimental to Canadian patients and, for some, would mean the difference between getting treatment when it could make a difference, or not.

We recommend that the PMPRB take advantage of this proposed review of mandate and regulations to more fully explore, with all stakeholders, alternative pathways that would lead to the triple goal of meeting patient needs, supporting investment in innovation, and assuring non-excessive pricing. To that end, CORD offers the following recommendations to guide this process.

1. PMPRB should provide incentives or at very least not put Canadian patients at disadvantage for early access, including clinical trials and regulatory filing
2. PMPRB procedures should be as streamlined as possible, that is, minimize bureaucratic hurdles and red tape, to assure no unnecessary delay and cost and promote willingness to trial and market drugs in Canada
3. Mechanisms of setting prices and conditions for access and monitoring should be as transparent as possible with public accountability
4. Pricing negotiations should allow for patient-centred access approaches that would optimize the opportunity for all patients who may potentially benefit from therapy to have access, for example, through risk-sharing, managed access, early access, or compassionate trial programs

## Key Concerns with Proposed PMPRB Process

### Singular Focus on Prices Means Negative Impact on Access and Prices

It is unconscionable that the Regulatory Impact Analysis Statement RIAS did not explicitly include assessment of the impact of the proposed amendments on patient access to medicines. It is not a sufficient defense to argue that access is not the responsibility of the regulator or to propose that the PMPRB's sole mandate is to police excessive pricing, not to consider therapeutic value. Indeed, without a firm commitment to patient access, which is the only reason for a drug policy and programme, there is no context for determining whether the amendments to the Patented Medicines Act are helpful or harmful. The drug access environment, like a three-legged stool, is only functional and steady if all three objectives are balanced.



These objectives are: timely (individual) patient access to medicines appropriate to patient needs, continued investment in innovation to develop better therapies, and drug pricing appropriate to value of the medicines and funding resources.

### **Lack Search for Win-Win-Win Solutions**

We must consider how and to what degree the revised policies and procedures, which put downward pressure on initial drug prices (and subsequent drug costs), could result in poorer access to needed medicines or longer delays to clinical trials and access and the alternative solutions to manage inevitably rising drug budgets without blocking access to important new therapies for Canadian patients. We do not believe we should set up a system premised on “trade-off’s” between access and cost but one that seeks to find solutions to meet our collective and fundamental obligation to assuring sustainable access to “first in class” medicines to treat unmet needs, for therapies (including gene and cellular) that will prevent and cure chronic conditions, and for drugs and medical devices that will replace riskier and more invasive interventions. We need strategies that are forward thinking and not a “doubling down” on acknowledged failed processes by tightening down (external) reference-based price controls and introducing (internal) complex pharmacoeconomic evaluations (value-based pricing) to establish the initial ceiling price.

### **12-Country Reference Includes Those w/Slower and Poorer Access**

We have a lot of questions about how the steps outlined in the flowchart will work, whether singularly, sequentially, or in tandem. In terms of the first pass against the reference group of 12 countries, we are concerned because many new drugs are not available in some of these countries and in other cases some are launched considerably after their introduction in Canada. So now what? Canadian patients obviously should not be obliged to wait until there is a “median” benchmark price before introduction to Canada. (We were assured that this would not be the case but have no understanding how this rule would be applied.)

### **Traditional PE: Challenge of a Single \$/QALY Threshold**

Under the proposed amendments, drugs that meet the first hurdle of reference pricing will undergo a pharmacoeconomic (value-based) evaluation if they are identified as “high priority” based on a combination of factors: first in class, having few or no therapeutic alternatives, providing significant therapeutic improvement over existing treatment options, [indication for a condition that has a high prevalence in Canada], high cost or classified as a high priority ... because of unmet medical need.

Moreover, it is not clear from the scoping document if or how values other than economic ones are integrated into the establishment of the ceiling price. Perhaps we are reading too much into it, but CORD is very troubled by the use of the much

older term “pharmacoeconomic” evaluation, which focuses on factors expressed as economic values, rather than the more comprehensive approach denoted by “health technology assessment”, which (theoretically) is a multidisciplinary process that summarises “medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner”<sup>10</sup> and most importantly, incorporating patient preferences<sup>11</sup> in patients (for example, as measured by patient reported outcomes and impact.<sup>12</sup>

In 2013, the UK government mandated NICE to develop a process for “value based pricing”; however, NICE subsequently abandoned the task, concluding that their proposed (quantitative methods would not adequately reflect society’s differential value for new therapies for conditions of different severity or with varying benefits to wider society.<sup>13</sup>

Indeed, even CADTH has walked back from the position that a single “evidence-justified” cost-effectiveness (cost-utility) threshold across (most) conditions is feasible or even ethical. Certainly, most other countries, including most in the reference “basket” do not rely on a single CE threshold or even multiple CE thresholds.

### **Traditional PE: So Wrong for Rare Disease Drugs**

We are obviously troubled by the proposed screening criteria, which will guarantee every drug for rare diseases is included in this tier. There are several reasons why “value-based” pricing (pharmacoeconomic evaluation) at launch is problematic but the application is especially detrimental for rare disease drugs. First, if it is demonstrably difficult to establish a single “value-based” threshold across all conditions and therapies, it is nigh near impossible to justify an initial CE threshold for DRDs, even if there were differentiations (discounting factors) that would allow the threshold to rise (based, for instance, on severity or lack of alternatives).

In contrast to almost every other country, high or middle income, Canada has consistently been reluctant to recognize that drugs for rare diseases must be treated differently if patients are to be treated equitably. These differences cannot be subsumed into quantitative factors to modify a CE threshold. Not only are rare diseases, by definition, small patient populations, but most are also severe, debilitating or life threatening. Usually a new therapy not only addresses an unmet need, but it is also the first therapy for the condition, so there are no alternative treatments for comparison or substitution. Finally, a rare disease may also be highly variable in terms of causation, symptomology, natural progression, and response to therapy, all of which complicate the prediction of drug performance and long-term outcomes.

Drugs for rare diseases are not the same as “personalized” medicines for subgroups of more common diseases, which may have well-established disease trajectories, several alternative treatments, well-documented clinical outcomes or other predictors of long-term impact.

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Many DRDs are truly innovative, the result of breakthroughs in understanding of causative pathways, innovation in technologies, and creative new trial designs, none of which lend to application of traditional health technology assessment using traditional pharmacoeconomic models.

### Alternatives to PE and ICERs for Rare Disease Drugs

It is important to note that some of the countries in reference basket do not apply cost-effectiveness to assessment of orphan drugs.<sup>14</sup>

CORD agrees with the opinion of many health economists that traditional HTA methods applied to orphan (rare disease) drugs “capture the comparative clinical effectiveness or net health benefit of [these] new treatments.”

With respect to rare diseases, the proposition that ubiquitous qualifiers of “prolonging life” or “significant QALY gains” could serve as ameliorating factors for adjusting the \$/QALY would be challenging for drugs for rare diseases. Many DRDs lack the necessary evidence that would be derived from long-term experience, natural history or other indicators. As a result, any assessments would be shrouded by high uncertainty, based on the same reasons.

We note the following statements, which summarize the challenges for DRDs. “Orphan drugs have highly variable and unique circumstances specific to each disease and face methodological data constraints, including varying levels of available evidence, small study populations, quantification of quality of life benefit, rarely measured spillover effects in families, variation in cost-offsets that determine cost-effectiveness, high burden of illness, lack of appropriate comparator treatments, *etc.* ... heterogeneity in treatment options and characteristics of orphan disease patients cannot be addressed by a ‘one-size-fits-all’ assessment approach, and attempting to do so undermines the full value of these treatments.”<sup>15</sup>

Many other countries, including those in the reference basket, have adopted approaches other than traditional HTA to demonstrate the value of DRDs. For example, England and Scotland include “disease and treatment experiences from a multi-stakeholder standpoint”, combined with other measures to deal with uncertainty (e.g. managed entry agreements). This multi-stakeholder approach is reflected in pan European initiatives, such as the Mechanism of Coordinated Access to Orphan Medicinal Products,<sup>16</sup> that fosters multi-stakeholder dialogue and consensus about value determinants throughout the life-cycle of [a DRD].<sup>17</sup>

Sweden does not use PE/CE for DRDs but applies three principles for value determinations: a human dignity principle (all citizens should be treated equally despite personal characteristics or standing in society); a needs-solidarity principle (the health system should provide equal access to care for all and strive for optimized clinical benefit based on patient need); and a cost-effectiveness principle (the health system should strive for balance between costs and effect).

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While the Netherlands does perform HTA, they have no fixed ICER for DRDs.

Interestingly, Ontario is often noted as a jurisdiction where DRDs are not subject to HTA or ICER; rather a CEA is based on patients' ratings of quality of life moderated by other factors, notably severity of disease and level of disability. Sadly, the Ontario DRD committee and process has been inactive for several years.

As importantly, as a patent community, we are frightened by the apparent retreat under the proposed amendments for any commitment to investment in innovation (R&D), premised ostensibly on the inability of the PMPRB with current procedures to assure a desired level of research and development. Without the continued investment of pharmaceutical manufacturers in innovative drug development, including clinical trials, Canadian patients will suffer from the lack of access to experimental therapies and the investment in clinical sites and disease management. We are not in a position to suggest the appropriate percentage of R&D investment but we do not know that companies and investors are attracted to environments favourable to business investment. We suggest that Canada could go a long way to creating a more favourable R&D environment for innovative pharmaceutical research, such as the Orphan Drug Act that was passed in the USA, in Europe, in Japan and other countries.

### **Recommended Steps Forward**

We are at critical juncture for action. The proposed amendments to the Patented Medicines Act have propelled all stakeholders to acknowledge the current drug access system is broken and there is an urgent need for transformation. CORD believes, based on the pre-submission dialogues we have hosted as well as other conversations, that stakeholders do not feel there has been adequate exploration of all options for designing a system that meets our mutual goals for timely appropriate access, investment in innovation, and sustainable financing. Therefore, CORD offers the following next steps:

1. Immediately withdraw the proposed Amendments to the Patented Medicines Act and cease all consultations on them.
2. Convene a gathering of leaders representing all stakeholders (and sectors) to develop a focused, goal-directed, and time-limited engagement process that could include open meetings, requests for white papers and briefs, expert multi-stakeholder dialogues (including patient experts and international experts), and other forms of deliberation and collaboration with the objectives of surfacing principles for patient-centred, responsible, innovative, and sustainable pharmacare, international best practices, opinions, innovative approaches, collaborative win-win-win options.
3. Propose viable alternatives for focused deliberations leading to consensus on a viable lifecycle approach to providing access, promoting innovation, and assuring financial sustainability of medicines in Canada.

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## About the Canadian Organization for Rare Disorders (CORD)

CORD is the Canadian Organization for Rare Disorders, Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada.

1 in 12 Canadians has a rare disorder. Many others are affected or at risk but remain undiagnosed and unaware. CORD provides information to individuals and connections to other rare disorder support groups and organizations from Prince Rupert, British Columbia to St. John's, Newfoundland.

CORD has led the development of Canada's Rare Disease Strategy, bringing together experts from every sector. The Strategy details the extraordinary burden faced by Canadian families with rare illnesses. The Strategy proposes a five-point action plan that will address unnecessary delays in testing, wrong diagnoses and missed opportunities to treat. CORD is a key partner in the design and implementation of Ontario's Rare Disease Strategy and Framework.

CORD has been active in shaping's Canadian Orphan Drug Policy, including drafting of the federal government's proposed Canada's Orphan Regulatory Framework, the Provincial/Territorial plan for Expensive Drugs for Rare Disorders, and implementation of Canada-wide standards for Newborn Screening. CORD partners with the Canadian Institutes for Health Research to support funding for innovative research in rare diseases and is working to ensure Canada's Clinical Trials Registry works effectively for those with rare disorders. CORD is partnering to promote timely genetic screening and diagnostics to reduce time to accurate diagnosis and supports development of Centres of Expertise for Rare Diseases linked to regional and local services to facilitate best-practice treatment, care and support.

CORD links patients with one another and with support groups. CORD links patient groups with researchers, companies engaged in drug development and clinical trials, agencies reviewing drugs and other therapeutic interventions, payers for health services including drugs, and policy makers to ensure patient-centred health services and allocation of resources.

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