Report on the incompatibility of the proposed PMPRB guidelines with the perspective of patients/caregivers and the future of new launches of drugs for rare disease (DRDs) in Canada

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Introduction

The PMPRB released draft guidelines for final stakeholder consultation in June 2020.[1] Significant opposition to various iterations of the guidelines has been shared with the PMPRB by Patient Groups, Industry Associations, and individual pharmaceutical/biotech manufacturers, among others.[2] Some themes of the critique are consistent: there is too much unpredictability in price setting for all medications and it would be particularly difficult for manufacturers to bring drugs for rare diseases (DRDs) to the Canadian market thereby unfairly punishing people with orphan diseases. Justification for the revised guidelines appears to have been based, at least in part, on a PMPRB report entitled "Insight into the spending on expensive drugs for rare diseases".[3] The purpose of this review of the report and the draft guidelines was to determine if concern over DRD pricing is objective and warranted.

Methodology

Four key analyses were performed as follows: (1) findings of the report were critically appraised to determine if the conclusions are evidence based; (2) the guidelines were assessed to evaluate whether DRD pricing would be unduly disadvantaged; (3) a revised analysis of the historical DRD public expenditure was prepared to contrast with the PMPRB analysis; (4) DRD costs were compared vs. other expenditures to provide perspective.

A. Critique of the PMPRB Report: "Insight into the spending on expensive drugs for rare diseases"

Each page of the PMPRB's report was critically appraised to evaluate whether there could be bias in the methods or findings of the analysis and/or whether an alternate interpretation was plausible.

B. Assessment of the Draft PMPRB Guidelines

The proposed price setting factors were reviewed in a qualitative manner to determine whether there would be barriers to market entry of DRDs.

C. Alternate Analysis of Historical and Future DRD Expenditure Projections

Identification of DRDs

A comprehensive search was performed. Currently available drugs were screened from the EMA Community Register of Orphan Medicinal Products[4] and two peer-reviewed Canadian publications.[5,6,] Future pipeline drugs were screened from the Pharmaceutical Research and Manufacturers of America (PhRMA) Medicines in Development for Rare Disease report.[7] The inclusion and exclusion criteria for the identification of DRDs are presented in Figure 1. Treatments for oncology indications were excluded because, unlike medications for rare diseases, oncology treatments are used for a more limited duration and they are usually approved for more than one indication.

Quantification of DRD Expenditures

Historical expenditures for DRDs currently funded were obtained from claims data.[8] Historical costs were extrapolated in a linear manner out to 2025. Future expenditures for pipeline DRDs expected to reach the Canadian market were also projected to 2025. Extrapolations were based on development phase, expected year of public funding, prevalence, and expected weighted average annual cost. The total projected DRD costs to 2025 were then compared with the total public expenditures for all drugs (CIHI; 2014 to 2018)[9] projected to 2025.

D. Comparison of DRD Costs with Other Expenditures

Annual Canadian expenditures for treatment of smoking-related illnesses, cosmetic procedures, recreational cannabis, alcohol, and total healthcare costs were compared with the annual Canadian DRD expenditure.

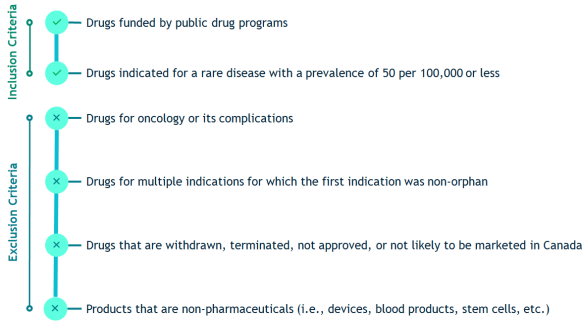

Figure 1: Inclusion and exclusion criteria used for screening DRDs

Results

A. Critique of the PMPRB Report

The language used to describe the findings does not appear to put the results into context with the challenges faced in the development of DRDs, the increasing costs of any other drug segments, or the total cost of DRDs relative to other areas of healthcare spending for non-rare conditions. Our review revealed that the main conclusions of the PMPRB report are not supported by evidence and are provided without needed perspective. The conclusions and additional perspective are shown in Table 1.

Table 1: PMPRB report conclusions in comparison with missing perspective

Conclusions	Missing Perspective
"Orphan medicines are dominating landscape"	**Lacks comments on:** • **fact that diseases were previously untreatable** • **patient/caregiver perception of value as life changing or life extending**
"…pushing the limits of affordability"	• Costs of the 42 DRDs account for only 2.5% of the total pharmaceutical sales • Actual prices paid are much lower than the list prices due to confidential agreements • Payers are involved in the collaborative decision regarding the net price • Mechanisms in place to ensure value is achieved and risks of exceeding projections are minimized • Annual cost of DRDs (~$280M) pales in comparison with costs of smoking-related illness and obesity ($6.5B and $8.8B, respectively)
"…limited or unclear therapeutic benefit"	• **The drugs are approved through Priority Review mechanism due to lack of available alternatives** • **Low patient numbers in trials due to disease rarity** • **Lack of consistency between research reports (Board Staff/Drug Information Centre) designating drugs as "breakthrough" vs recommendations downgraded by the expert committee (HDAP)**
"…spending…is above the OECD norm"	• Canada's expenditure appears to be at or below the norm when looking at orphan drugs only • Context of heredity of rare disease and our more heterogeneous population; is expenditure in line with proportion of population afflicted?

B. Assessment of the Draft PMPRB Guidelines

Numerous aspects of the current version of the Proposed PMPRB Guidelines must be altered in order to ensure that Canadians will continue to have access to these important medications. The pharmacoeconomic value threshold (PVT) and the therapeutic criterial level (TCL) tests disadvantage DRDs, especially those that target ultra-rare diseases as follows:

- Some DRDs are known to target only 10 patients in Canada; it will be highly unattractive for manufacturers to bring drugs to market if the target ICERs are $200,000 or less and the market is exceedingly small.
- The majority of DRDs may fall into the moderate to little or no additional value categories due to the lack of ability to conduct large randomized controlled trials. If the PMPRB deems that the evidence supporting the treatments is "limited", the applicable rebate price could be untenable.

C. Alternate Analysis of Historical and Future DRD Expenditures

The total public drug plan expenditure for DRDs grew from $79M in 2014 to $235M in 2018. From 2014 to 2018, total public drug expenditures in Canada increased from $11.4 to $14.4 billion. Expenditures for the funded DRDs as a proportion of total public drug expenditure increased from 0.7% in 2014 to 1.6% in 2018. The future public expenditures are anticipated to be $280M in 2019, growing to $1,394M in 2025 (Figure 2A). The anticipated annual expenditures for DRDs represent 1.9% of total public drug expenditures in 2019, increasing to 6.5% in 2025 (Figure 2B).

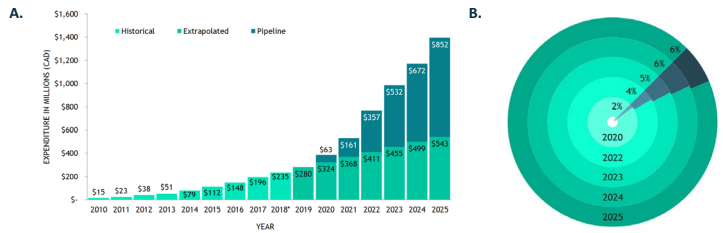

Figure 2: A. Historical and future public expenditures on DRDs. (*) Claims data was available until Q3 for 2018 and adjusted to account for Q4. **2B.** Total annual DRD expenditure in Canada as a percentage of total pharmaceutical spend.

D. Comparison of DRD Costs with Other Healthcare and Non-Healthcare Expenditures

While the per patient cost of DRDs may seem high compared with the costs of drugs for common conditions, the overall public expenditure for DRDs is minimal when placed in context with other public and consumer expenditures. The total cost of other medications for non-rare conditions vastly exceeded the cost of the DRDs. Similarly, common Canadian government and consumer spending eclipses public DRD spending (Figure 3).

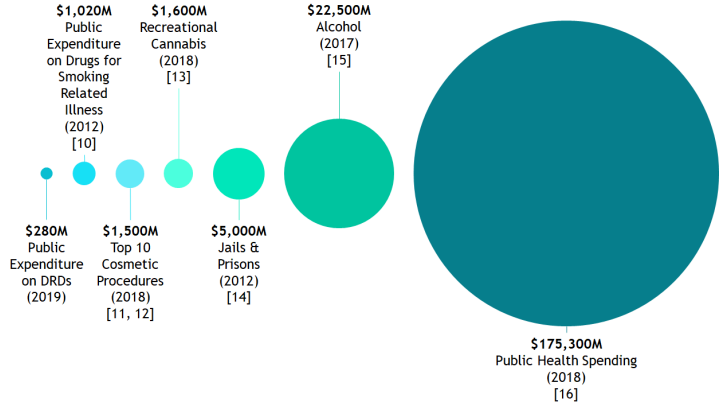

Figure 3: Comparison of the public DRD expenditure to other government and consumer expenditures

Discussion

Concerns regarding unsustainable growth in Canadian public drug expenditures driven by DRDs may not be justified. New PMPRB guidelines particularly disadvantage DRDs due to the additional tests of TCL and PVL. Studies examining the cost and value of DRDs are particularly pertinent given the current policy climate in Canada, including the federal government's recent announcement of dedicated funding for a national strategy for DRDs. While stating that a National Pharmacare strategy will have a core principal of "Comprehensive, evidence-based formulary, with special consideration for drugs for rare diseases"[17], it is clear that the new PMPRB guidelines provide the opposite of "special consideration".

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Presented at the 2020 Annual Meeting of the Canadian Association of Population Therapeutics, Oct 26-27, 2020

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