I am pleased to be able to offer feedback on the scoping paper for the Board's guidelines. I am a physician with expertise in rare inherited metabolic diseases. I have provided consultative services in the area of rare diseases for CADTH and Health Canada and have also participated in PMPRB and pCPA consultations around high cost drugs for rare diseases. I am the medical lead for rare diseases with the BC Provincial Health Services Authority where I provide advice to the BC Ministry of Health. Finally, I am a member of the Implementation Advisory Group for the National Strategy for Drugs for Rare Diseases.

Given my background, I have reviewed the scoping paper and make the following comments specifically with the lens of rare diseases. The opinions I express are my own and I am not speaking on behalf of any of the groups with whom I consult.

1. **Theme 1 – Price monitoring**
    a. I agree with continuing to categorize medicines by level of therapeutic improvement. However, for rare disease drugs where there is often no alternative therapy, slight improvements may be given disproportionate weight and some index of "clinically significant improvement" would be useful.
    b. One key issue with Theme 1 is the use of list prices for comparison. Data on actual prices should be used. I give a recent example in Canada of enzyme replacement therapy for Gaucher disease. The prices of these were not flagged under the PMPRB guidelines as list prices were comparable. However, the Canadian Gaucher physicians became aware that the actual prices were much lower in other countries. The provinces were able to obtain some of this information from other jurisdictions and initiated negotiations that reduced the price of the drugs in Canada by almost 50%. I realize that accessing current confidential pricing agreements made by manufacturers with other countries will not usually be possible. However, a review of the history of past agreements (which presumably are no longer confidential) within the PMPRB11 could give guidance on what the average discount from list price is for the various countries for different therapeutic classes. This review could be updated on a rolling basis. Knowledge of that average discount could then be used to inform price comparison even though that data on average discount may be somewhat out of date.
        i. Note that a rolling review of average discounts might help Canada to avoid the upward trend shown in Box 3 of the report.
    c. Given the limitations of list vs actual prices, I would suggest MIP be used as the triage measure as, once discounts are taken into account, even the MIP might be much higher in Canada.
2. **Theme 2 – New versus existing medicines**
    a. I would suggest that the guidelines apply to both new and existing medicines. For existing medicines above the HIP, review should occur as soon as possible. Given the logistical challenges, I would suggest triaging those reviews according to total budget impact
3. **Theme 3 – Price reviews**
    a. Price reviews should be different for medicines for rare diseases where drugs come on to the market with high levels of uncertainty about their safety and efficacy. For drugs that have time limited recommendations by CADTH, the review should come at the time that the TLR is reviewed (eg. 3 years).
    b. The information in Box 3 is justification for reviewing both small molecules and biologics during their life cycle (eg. Every 5 years). All of the criteria under Question 3.2 are relevant.
    c. Drug prices are not influenced by market forces but rather willingness to pay. For this reason, I don't think that the Consumer Price Index should be a consideration. All the jurisdictions in the PMPRB11 are subject to inflationary pressures. Canada should not continue to pay more while the others pay less as shown in Box 3.
4. **Theme 5 – Relation to other stakeholders**

a. Obviously, coordination with the other agencies involved in getting drugs reimbursed for Canadians is desirable. However, specifically I would highlight the fact that the PMPRB needs to know in real time what the actual price of the drug will be (based on the results of the pCPA negotiations) in order to determine if pricing is excessive. Similarly, if private insurers are getting better prices than pCPA, coordination amongst the agencies could strengthen bargaining position
b. A key function of PMPRB is the jurisdiction scan for pricing and this is one way PMPRB could really help the other stakeholders involved. As discussed above, getting as much information as possible about actual prices (discounts, rebates etc), even if that information is not up to date, would be of value. So, for example, if the PMPRB11 had average discounts from list price of 40% for the time interval of 2016-2020 and the pCPA negotiations averaged 30%, then the relative price for evaluation by PMPRB would be 10% higher. Rolling review of discounts might show that the average discount increase over time and, although the PMPRB may never be up to date with the exact discounts of the PMPRB11 (due to confidential pricing agreements), being 2 years out of date on actual pricing is still likely to be more informative than to rely on list pricing only.
    i. If changes to PMPRB policies are required to allow collection of data on actual prices, then legal supports for those policy changes should be prioritized.

5. Theme 6 – Engaging with patients, health practitioners, pharmacy and other stakeholders

a. I have extensive experience with innovative medicines for rare disease in Canada, having been involved with the launch of every therapy for inherited metabolic diseases since 1998. With this experience, I am aware of several factors;
    i. Canada regularly pays more for rare disease medicines than other countries with socialized health care systems. I have cited the example of Gaucher disease above. Another example is that of a drug used for inpatient treatment of hyperammonemia (sodium phenylacetate/benzoate) which, in Canada, costs ~$1000/hr to infuse (adult dose) whereas my colleagues in the UK use this for <$100/day.
    ii. Lack of communication amongst various agencies (CADTH, pCPA, PMPRB, Health Canada and the provincial/territorial payors) makes some of these problems worse. As an example, all Canadian patients with cystinosis used to use cysteamine eye drops which were compounded at hospital pharmacies with a cost of ~$500/year. Health Canada approved a proprietary formulation (Cystadrops) at $105 000/year. As pharmacies are not allowed to compound drugs when proprietary formulations are available, this price increase had to be borne by the provinces. Had there been discussions among Health Canada, PMPRB, pCPA and the provinces before the drug was given NOC, the conclusion of those discussions could have been that NOC was not granted, allowing the provinces to use the existing therapy. There are other similar examples (eg. Procysbi, Cystadane) where lack of communication amongst these stakeholders resulted in price increases for exactly the same active drug of more than 1000 fold.
    iii. A regular discussion point raised during discussion of rare disease drug pricing is the need for innovation. However, if one looks at the trajectory of rare disease drugs, we see that companies are not innovating in that >95% of ultrarare diseases still have no drug therapy options whereas companies continue to develop drugs for the same “less rare” diseases. So, the role of incentives (such as those in the US Orphan Drug act) to stimulate innovation needs review so that such incentives are applied only to true innovation and not “me too” or “evergreening” products
    iv. Price regulation has been cited as a disincentive for manufacturers to invest in clinical trials in Canada. However, given that Canada has the worst ratio of R&D to sales amongst comparator countries, I would suggest that this “ship has sailed”. While I have been involved in many clinical trials, I am aware that the geography of Canada is such that it will never be a desirable place for trials (regardless of price regulations or not) – having a small

population set across vast distances will always make trials very expensive to run in Canada and this is not a problem that can be fixed.

v. There has been concern raised by industry and patient support groups that price regulation will reduce the incentive of manufacturers to bring drugs to the small Canadian market. However, other smaller countries have lower prices and there is also the option for Canadian payors to buy from other countries (through the Special Access Programme) if manufacturers choose not to bring drugs to Canada. To try to guard against this issue, I believe review of compulsory licensing laws would be useful to allow those laws to be linked with PMPRB determinations of excessive pricing.

b. I believe that conflict of interest guidelines with respect to groups that consult with all agencies (including PMPRB) should be updated. In the rare disease world, there are advocacy groups which might only have 1 or 2 manufacturers supporting them (as there may only be 1 or 2 companies interested in that disease) and it is difficult for those groups to have an independent voice. While the individual who provides the input might not be receiving money personally, there is still considerable potential for bias based on the funding of the group. This issue also extends to individuals who represent "institutes" where the "institute" is funded by industry. Full disclosure of all sources of funds for both the individual providing input AND the group that this individual represents should be required.

As I final note, I am aware of court decisions (eg. In the case involving Soliris) where the ability of the PMPRB to protect Canadians against excessive prices was restricted due to legal limits of their defined mandate and the patent act. However, it is notable that the Federal Court of Appeals did not disagree with the determination that Soliris was excessively priced but rather the ruling was based on what parameters govern the PMRPB. I believe that most Canadians would be shocked to see that the courts do not feel the mandate of the PMPRB includes consumer protection. This is a fixable problem. The mandate of the PMPRB should be revised to include consumer protection. I hope there is the political will to get this done.

Thank you for the opportunity to give feedback. I would be happy to answer any questions that might arise from this feedback (Sandra.Sirrs@vch.ca).

Sandra Sirrs