Merck Canada Inc.

Response to Consultation Request - PMPRB Draft Guidelines

February 14th, 2020

1. Executive Summary

Merck Canada Inc. (Merck) appreciates the opportunity to provide feedback on the draft Guidelines developed by the Patented Medicines Prices Review Board (PMPRB) to operationalize the changes made to the Patented Medicines Regulations.

With this submission, Merck intends to complement those developed by our industry associations Innovative Medicines Canada (IMC) and BIOTECanada (BTC), which we have contributed to and support. The PMPRB should not interpret this submission as supporting the mandate of the PMPRB, the provisions of the Patent Act relating to the PMPRB, the Patented Medicines Regulations and the draft Guidelines. We reserve the right to challenge any aspect of the PMPRB, its legislation, regulations, policies and guidelines in a court of law.

That said, and while we continue to object to the changes made to the regulations and the rationale for these changes, we understand that the consultation process for the PMPRB is focused on the translation of the regulations into Guidelines. In this submission, we provide constructive feedback to help minimize the negative impacts of the Guidelines on patient access to medicines, clinical trials and the biosciences ecosystem. As well, we want to contribute in a positive way to this consultation to help put in place clearer Guidelines to promote better compliance by patentees. Well-defined Guidelines will also ensure better use of public resources and reduce the regulatory burden on patentees.

In this context, we want to start by emphasizing the fact that the draft Guidelines go much further than what is needed to achieve the savings contemplated by Health Canada. A recent analysis by PDCI Market Access shows that the financial impact of the pricing reform on the industry will be nearly five times more than what Health Canada forecasted when it made the regulatory amendments or the equivalent of $41.8 billion revenue decrease on a base of $150.8 billion or 27.7% reduction versus 5.8% quoted by Health Canada. Such a drastic and sudden financial impact will end up unnecessarily curtailing patient access to medicines and reducing clinical trials and employment.

We already see these impacts materialize across the Canadian industry, including at Merck, where we have had to cut back on our workforce by 30% in November 2019 and pause our decisions to launch certain medicines. We need the PMPRB to scale back the draft Guidelines before implementation. Once the Guidelines are in place, it will be very challenging to undo the harm caused to patients and the health system. It will take years to rebuild a market that attracts early launches of medicines and global investments in clinical trials.

The most problematic aspect of the draft Guidelines is the routine application of economic factors. In particular, pharmacoeconomic (PE) factors are inappropriate for setting price

ceilings. PE factors are highly variable and subjective estimates, which will make it impossible for patentees to predict what prices are deemed acceptable in Canada, and possibly lead to unsustainable pricing overall. As for the market size factor, it is an arbitrary revenue-control tool that is completely disconnected from price excessiveness determinations. A pragmatic solution that is aligned with the regulations would be to restrict the use of the economic factors to exceptional circumstances only (e.g., within board hearings to determine whether a price is excessive).

Our submission demonstrates that there are many practical challenges regarding the implementation of the draft Guidelines in Section 3. We suggest that technical working groups have been shown to best address these kinds of challenges in the past and are very relevant in this situation. These technical working groups would tremendously benefit from industry representatives who are responsible for compliance activities and who have in-depth knowledge of the pharmaceutical contracting environment in Canada.

There is also an immediate need for bolstered transition provisions to address the entire Canadian pharmaceutical industry ecosystem. Given the magnitude of the reform, the transition provisions need to be augmented to implement the changes more progressively. Companies, including patentees and their suppliers, need to be provided with a reasonable period to adjust their business models. These companies also need more time to adapt to the new rules to ensure better compliance. Specific suggestions on how to enhance the transition provisions are outlined in Section 4, including the adoption of fixed maximum annual price reduction limits.

Our submission makes additional recommendations to help achieve more balanced and operational Guidelines. These recommendations are anchored on a set of principles outlined in Section 5, that include, 1) Maximizing Canada in the middle of the basket of 11 countries, 2) Utilizing a risk-based approach, 3) Balancing the approach, and 4) Creating bright lines for operationalization and enhance compliance certainty:

- **Instituting a maximum reduction for economic factors**: In Section 6, we recommend a pricing floor for the MRP. The floor is needed to provide a level of predictability to patentees and to ensure prices are not set at unsustainable low levels.
- **Utilizing the highest price of the therapeutic class comparator (TCC)**: In section 6, we recommend using the highest price of the domestic and international TCC instead of the median when setting the Maximum List Price (MLP). Given this is the standard in the current guidelines, the highest of the TCC is tried and tested and is well understood by patentees. It is also more aligned with the PMPRB's mandate of ensuring prices are not excessive.

- **Other suggested changes**: In Appendix A, there is a list of other items that require less explanation but could help improve predictability and reduce systematic investigations and enforcement.

We hope that the PMPRB will carefully consider our recommendations as well as those of our industry associations to arrive at a workable pricing framework. We need a framework that leads to more reasonable and predictable drug price ceilings along with appropriate transition measures to ensure they are applied progressively, in a staged manner.

2. The Fundamental Concerns with the Proposed Draft Guidelines

Throughout the period between Canada Gazette I and Canada Gazette II, relating to the federal pricing reform, Merck has been signaling its concerns about the serious impacts the price reform will have on patient access to medicines, research investments and employment in the life sciences industry in Canada. Unfortunately, the draft Guidelines go even further than what we had anticipated, both in terms of setting unsustainably low price-ceilings and in introducing excessive levels of pricing uncertainty.

While Health Canada forecasted an $8.8 billion (5.8%) revenue decrease over ten years in its revised Cost-Benefit Analysis[1] accompanying the regulatory amendments, a recent assessment of the impact of the draft Guidelines shows a much greater revenue decrease of $41.8 billion of $150.8B or 27.7% reduction over the same period[2]. As well, a recent case study analyzing the impact of the draft Guidelines finds that prices will likely have to be reduced by 45% to 75% to be compliant with the new pricing rules[3].

Further, companies will not be able to reasonably predict at launch time the actual maximum price they can charge for their medicine. Before deciding to commercialize a therapy in a market, pharmaceutical companies need to be able to forecast the approximate revenues the product will generate. This forecasting is not possible based on the proposed pricing framework.

The projected revenue loss combined with the heightened business uncertainty will force pharmaceutical companies to reconsider drug launches, research investments and employment in this country. According to a recent survey of life sciences leaders, 97% indicated the PMPRB changes would negatively impact drug launches and employment and 91% indicated it would negatively affect clinical trials[4]. Already, at Merck, we had to make the difficult decision of laying off 145 people in November 2019, driven in large part by the PMPRB changes, which represents 30% of Merck's Human Health workforce. We have also paused our decisions to launch certain medicines and are looking at delaying the launches of others in Canada in key therapeutic areas, including oncology.

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[1] Amendments to the Patented Medicines Regulations, Cost-Benefit Analysis, Strategic Policy Branch, Health Canada, May 6 2019 (page 50)

[2] Impact analysis of the draft PMPRB excessive price guidelines, PDCI Market Access, February 12, 2020 (page 2)

[3] Rawson N., New Patented Medicine Regulations in Canada: Updated Case Study, Canadian Health Policy Institute, January 2020: https://www.canadianhealthpolicy.com/products/new-patented-medicine-regulations-in-canada--updated-case-study-.html

[4] https://lifesciencesontario.ca/wp-content/uploads/2019/12/PMPRB-survey-interim-Report-2019_12_08.pdf

One of the most problematic aspects of the Guidelines is the new economic factors and the way the PMPRB is proposing to apply them. The PMPRB has an unreasonably broad level of discretion to reassess a medicine and reapply the economic factors throughout the product life cycle, driving further pricing uncertainty, and this well beyond the excessive pricing standard, as reflected in the Patent Act. Specifically, the pharmacoeconomic (PE) factors and market size factors used, as outlined in the draft Guidelines, in formulas for establishing price-ceilings are excessive for the following reasons:

For PE factors:

- The PE analysis and the use of incremental cost per quality-adjusted life-year (QALY) are inappropriate tools to regulate prices. The tools were developed to help guide evaluations and reimbursement decisions, which is how they are used internationally by other countries, and the use of the tools by the PMPRB are misguided in a price-setting context.
    - Cost-effectiveness analyses are subjective and vary significantly based on the assumptions and time horizons used, which are at the total discretion of the Canadian Agency of Drugs and Health Technologies (CADTH) and Institut national d'excellence en santé et en services sociaux (INESSS) when they calculate the Incremental Cost-Effectiveness Ratios (ICERs). Even within these two Canadian entities, the results of their evaluations differ. However, these are the same ICERS that the PMPRB is proposing to rely on to set a fixed ceiling prices.
    - CADTH and INESSS typically report ICER estimates as a range rather than a single figure. Moreover, as ICERs are comparative measures, they are produced versus all comparators. For example, if a new drug was compared to 10 drugs, then CADTH and INESSS would report 10 price-setting ranges of ICERs, to cover the 10 price comparisons.
- The use of cost-per-QALY thresholds is controversial even in a health technology assessment (HTA) setting, and CADTH or INESSS have not officially set a standard. Although not official, past recommendations by CADTH and INESSS have evaluated cost-effectiveness for specialized and oncology therapies against a much higher threshold than the one proposed by PMPRB (e.g. $100K to $150K per QALY for oncology medications). The use of the higher threshold is because cost-effectiveness analyses do not accurately reflect the value of specialized therapies, including oncology medicines, due to data availability issues. As a result, it is unlikely that such medicines would meet the stringent threshold proposed by the PMPRB.
- CADTH adopts a public healthcare perspective. As a result, their analyses fail to incorporate important factors of value that apply to the general population (e.g., indirect economic impacts).

For market size factors:

- The market size factors are completely irrelevant and disconnected from the notion of price excessiveness. How the PMPRB is proposing to use these factors to further ratchet down prices amounts to revenue control. This approach will end up unfairly penalizing companies that bring ground-breaking treatments to the market that address unmet medical needs and certainly treatments that could benefit a large number of patients.
- The market size factors will lead to annual fluctuations of price ceilings. These fluctuations will create uncertainty and impose a significant operational burden on companies and the pan-Canadian Pharmaceutical Alliance, as they will have to continuously adjust pricing agreements as a result of the annual price ceiling reductions.

The PMPRB does not need to incorporate these economic factors in the routine calculation of price ceilings to achieve the savings contemplated by Health Canada. While we continue to believe that the government should completely remove economic factors from the regulations, we understand that this is not within the purview of the PMPRB and these consultations.

However, the PMPRB could decide to restrict the use of economic to exceptional circumstances (e.g. within board hearings to determine whether a price is excessive), to ensure PMRPB does not end up unnecessarily curtailing patient access to medicines, reducing clinical trials and employment and negatively affecting the broader biosciences ecosystem.

3. The Path to Practical Guidelines

If the PMPRB continues to proceed with the implementation of the Guidelines with the routine application of economic factors, Merck must explore all possible avenues to improve the Guidelines.

Merck understands that the PMPRB intends to update its Guidelines within the framework of the amendments to the Patented Medicines Regulations, which are not yet in force. While Merck is committed to constructive engagement with the PMPRB on the draft Guidelines, Merck's participation in this consultation is not intended and should not be interpreted as supporting the amendments to the Regulations. Merck continues to have grave concerns about the practicality and legality of the amended Regulations, which are the subject of the ongoing legal challenge. Merck reserves the right to oppose any aspect of the Guidelines that exceeds the jurisdiction of the Board under the relevant legislation.

Hence, Merck met with members of the PMPRB on January 10th, 2020, to present our recommendations for the Guidelines that will improve the implementation and will improve the ability of the industry to comply with the Guidelines, ultimately improving the timely access to medications for patients in Canada.

In broad terms, Merck is looking for 1) transition provisions for grandfathered products, 2) a provision for a maximum reduction for the maximum rebated price (MRP) and 3) the use of the highest price of the domestic and international therapeutic class comparator (TCC) instead of the median price of TCC in setting the MLP. We will discuss all of these in further detail in starting in Section 4 below.

However, another important point raised by Merck is the practical challenges in complying with the Guidelines in their current form. For example, in the compliance for MRP, here are some of the considerations raised:

1. CADTH evaluation of products can take over six months post-NOC before there is a completed evaluation of the variables used in the PMPRB pharmacoeconomic price (PEP). There is the potential for sales before the evaluation of the setting of the MRP target.
2. The pCPA, which is the largest buying group in Canada, can take up to 18 months to negotiate a letter of intent, which is not binding because each jurisdiction must contract independently with the company. The contracting process with the individual jurisdictions after the letter of intent from pCPA can take months. Meanwhile, there are some provisions in provinces to cover special needs patients (e.g. patient d'exception in Québec). These purchases would be made at list price until the contract is consummated and hence would not be at MRP. Compliance

with the MRP targets could not occur until the completion of the contracting process.

3. The private insurance industry includes over 30 companies, and the timing of the contracting process can be challenging. The language in each contract must be scrutinized and agreed upon by both parties. Also, private insurance companies are competing among themselves and expect differential pricing, making it very difficult to manage meeting the MRP since the contracting will occur at different times.
4. Many private insurance companies have a multitude of group benefit plans, with some plans mimicking the provincial reimbursement timing and others reimbursing immediately before any contract pricing. The various timing could cause issues in complying with MRP.
5. Once all the contracting is complete, there remains the issue of timing of invoices from all the contracting parties — some invoice monthly, some quarterly, some semi-annually and yet some others annually. Any material invoice not included in the period of reporting could misrepresent compliance with the MRP targets.
6. Finally, some customers do not renew contracts, especially in the situation where the product is subject to tender and Merck is not the winning bidder. If the contract is terminated, the speed to comply to MRP as the business re-adjusts could be challenging.

Hence, Merck believes that the only way to work through these questions would be the implementation of technical working groups, with robust industry participation, including representatives from manufacturers / companies that are responsible for the actual compliance activities and that have in-depth knowledge of the contracting environment in Canada. The concept of technical working groups has been utilized in the past by the PMPRB[5] and once again, would provide the opportunity to generate practical solutions based on the realities of the pharmaceutical industry. As in 2011 and 2012, the legitimate consideration of the recommendations[6] from the technical working groups is paramount to workable Guidelines.

[5] DIP Methodology Technical Working Group - March 2011

[6] Follow-up Recommendations on Implementation of the DIP Methodology, April 2012

4. The Need for Transition to Address the Entire Canadian Pharmaceutical Industry Ecosystem

No other industry in Canada has ever faced such material and immediate change to their revenue stream from the implementation of government regulations. Other regulations were progressively implemented to address burden of compliance, such as the changes to Canadian Food Labelling, in which the food industry had a transition period of 5 years to make these changes[7]. Similarly, after the "ratification of the Canada-European Union Comprehensive Economic and Trade Agreement (CETA) and the Comprehensive and Progressive Agreement for Trans-Pacific Partnership (CPTPP) [the federal government made] available $1.75 billion over eight years to Canada's nearly 11,000 dairy farmers"[8],

The industry is much more able to comply with the implementation of the new Guidelines if there are provisions for bringing in the changes more slowly over time:

1. We will need to scale back some of our investments because of the lower revenues, and the Canadian third parties that rely on our company (i.e. supplier ecosystem) would also need the time to adjust their operations. If pharmaceutical revenues are affected more slowly, the companies that depend on our funding, who tend to be principally local Canadian entities, will also be able to adjust their businesses to the changing reality.
2. Small and medium-sized Canadian based pharmaceutical enterprises do not benefit as much from global diversification of larger multinationals, and a sudden and rapid change in revenue could challenge their ability to maintain their operations.
3. All companies need time to adapt their business models to reflect the significant changes from the Guidelines. Some of the costs we need to adapt are linked to long-term commitments/contracts that would need to be re-negotiated.
4. In many of our customer contracts, there are triggering provisions linked to major market events. Major and rapid changes in pricing are more likely to trigger the major market events clauses and would lead to several renegotiations versus having more time to deal with contracts as they come to renewal.

[7] https://www.canada.ca/en/health-canada/services/food-labelling-changes.html

[8] https://www.canada.ca/en/agriculture-agri-food/news/2019/08/government-of-canada-announces-compensation-for-supply-managed-dairy-producers.html

As Merck understands, the PMPRB has clarified that the following be added to the Guidelines for the timing of compliance on grandfathered products (products with DIN's issued before August 21st, 2019):

1. Companies will need to report the transparent prices for all DINs in the 11 reference countries as of June 30th, 2020; due on July 30th, 2020. These prices will be used by the PMPRB to calculate the target MLP targets for all the DINs that apply.
2. Companies will need to report list prices for all DINs from July 1st to December 31st 2020 and units sold; due on January 30th, 2021
3. PMPRB will calculate excessive revenue for the period of July 1st, 2020 to December 31st, 2020, utilizing the updated 2020 Guidelines. However, no company will be asked to reimburse any excessive revenue calculated.
4. Companies will need to perform steps 1-3 for the periods of January 1st to June 30th, 2021 and July 1st, 2021, to December 31st, 2021. If companies comply with the targeted maximum list price set by PMPRB using the 2020 Guidelines by December 31st, 2021, no company will be asked to pay any excessive revenue calculated. However, if the company does not comply with the MLP target by December 31st, 2021, the excessive revenue calculated from January 1st, 2021 to December 31st, 2021 will require reimbursement.

These clarifications would appear to partly recognize our recommendation for transition provisions. To complete the recommendation for transition provisions, for 2022 and subsequent years, we suggest that there be fixed maximum annual price reduction limits (e.g. no more than 5% negative list pricing impact per twelve-month period under the new Guidelines). This would apply regardless of policy tool or the specific price test applied in Guidelines. For example, the PMPRB could benchmark a required total level of price reduction and require patentees demonstrate a 5% price reduction to be verified at the end of 2022, and so on, until the identified total price reduction requirement is met. This progressive implementation is fully aligned with the proposition made by our colleagues within the IMC submission.

5. Balanced Set of Principles to Provide Suggestions to Improve the Guidelines

In addition to the transition provisions, Merck is proposing other more impactful and significant improvements to the Guidelines, and to guide our recommendations, Merck developed four (4) guiding principles:

1. **Maximize Canada in the Middle of the Basket of 11 Countries:** The PMPRB specifically stated within the Guideline backgrounder that: "[we are seeking] prices of patented medicines in Canada that are more closely aligned with prices in like-minded countries"[9] and "[It is] Canada's responsibility to pay its fair share for global biopharmaceutical innovation"[10]. Anything in the Guidelines that prioritizes pricing in Canada that is close to the international median would be consistent with these stated. Any component of the Guidelines where the predominant situation would lead the lowest in the comparator group would not be consistent with this approach.
2. **Utilize a Risk-Based Approach**: PMPRB has stated on numerous occasions that there is an attempt to create a system where higher risk medications would have greater scrutiny, and lower risk medications would require less burdensome compliance[11]. This approach was already demonstrated with the reduction in reporting for generic medications and over the counter medications. Classifying medications that cost more than $25,000 per year as Category I in the presence of heavy competition would seem to violate this principle.
3. **Balancing the Approach:** It would be consistent with a balanced approach if, in the presence of price ceilings, then there would also be provisions for price floors. PMPRB has demonstrated a version of this in the establishment of maximum price reduction for the market size economic factor but has not established a maximum reduction for the pharmacoeconomic factors.
4. **Create Bright Lines for Operationalization and Enhance Compliance Certainty:** Guidelines without "bright line tests", would, "in the Board's opinion, not be in the best interest of the industry, the Board or the public. This approach would be

[9] https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/backgrounder-draft-guidelines-en.pdf (page 3)
[10] https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/backgrounder-draft-guidelines-en.pdf (page 13)
[11] https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/backgrounder-draft-guidelines-en.pdf (page 4)

expensive, time-consuming and confrontational rather than furthering the Board's objective of voluntary compliance"[12]. There should be a careful equilibrium between the ability for companies to consistently meet the requirements of the Guidelines and the efforts required by the PMPRB to monitor/enforce compliance. Guidelines that are predictable, transparent, and that maximize objective rules versus requiring interpretation will enhance compliance certainty.

In the following section, we will elaborate on Merck's two recommendations to improve the Guidelines that utilize these principles as a foundation.

[12] Bulletin, Issue No.5; Patented Medicine Prices Review Board; December 1989 (page 3)

6. Improving Predictability that will Reduce Systematic Investigations and Enforcement

Merck has generated several proposed changes to the Guidelines that could reduce systematic investigations and enforcement. These recommendations also aligned with the Health Minister's commitment to improving the affordability, accessibility and appropriate use of prescription drugs intended to improve the health of Canadians and better meet health care system needs. Consistent with the Minister's goal, the proposed recommendations below would provide high predictability of MLP and MRP for patentees during the launch phase that would result in increased probability of launches and more timely access to innovative medicines for Canadian patients.

First Priority Recommendation: Instituting a maximum reduction for economic factors

We have made several comments about the invalidity of using economic factors in the price-setting framework in Section 2 of this response. However, should the PMPRB Guidelines continue to be implemented with the routine use of economic factors, we are recommending a maximum total reduction of MRP from the use of the economic factors.

According to the current iteration of the Guidelines, category I products with a PEP can have their MRP adjusted downwards without any floor. Our recommendation for a maximum reduction represents a more balanced approach, that will have the benefit of addressing the PMPRB Board's intent while improving predictability for manufacturers and ease of compliance.

Defining *a priori* how low the MRP can go greatly improves predictability from a manufacturer's standpoint. With greater predictability comes the increased probability of early launches, as well as increased ability to comply. The MRP as currently outlined in the Guidelines is practically impossible to predict, and this is especially true for category I products with a PEP. As a result, manufacturers' ability to comply will be limited.

As discussed in the section "The Path to Practical Guidelines", the complex nature of negotiating and gaining access in Canada will make it virtually impossible for manufacturers to proactively comply with MRP. Introducing a maximum reduction on MRP will improve our ability to comply because we would at least have a sense of the lowest possible MRP and could proactively initiate negotiations with this floor in mind. The introduction of a maximum reduction will also improve probability of early launches in Canada, as it would enable local affiliates to provide reasonably dependable MRP estimates to global headquarters.

Another benefit of introducing a maximum reduction for MRP will be the ability for manufacturers and payers to keep negotiating listing agreements that better reflect the

concerns of these customers. Payers are increasingly negotiating to obtain expenditure predictability using mechanisms such as patient expenditure caps or total market expenditure caps. In addition, outcomes-based agreements are gaining in popularity but would expose the manufacturer to risk of compliance if the MRP is unpredictable or too low. To that end, when trying to determine an appropriate value for the maximum reduction, it will be important to identify a floor that is not so low as to deter any further negotiation between manufacturers and payers.

The best example we can provide for a recommended maximum reduction comes from the Ontario Auditor General report from 2015, which stated that Ontario collected rebates worth 30% of the brand sales[13]. Ontario is the largest public purchasing jurisdiction and fully participates in the pCPA, therefore exerts the most leverage of all Canadian purchasers. It is important to consider that the updated Guidelines already include a reduction of around 20% from the use of 11 countries[14], so the incremental effect from MRP would be 10% for a total of 30%. The numbers quoted in the Guidelines of up to 50% are well in excess of this 10% and of great concern for Merck.

Second Priority Recommendation: MLP calculated as the lower of 1. Median price of 11 comparator countries and 2. Highest price of the therapeutic class comparator (TCC)

The Guidelines propose a fundamental change to the therapeutic class comparison test. TCC is contemplated twice in the Guidelines as a domestic therapeutic class comparator [dTCC] and an international [iTCC] therapeutic class comparator.

The previous Guidelines used the "highest" priced comparator in the basket, i.e. the "top" of the TCC to set the maximum price ceiling; whereas the draft Guidelines are proposing to use the "median" of the TCC.

Merck is aligned with the IMC position to maintain the status quo of the highest price of the TCC, as it is a time tested and true method, and supports the principles of a predictable and balanced risk-based approach. The rationale for this recommendation is as follows:

1. *Highest of TCC would remain aligned with the PMPRB mandate of ensuring that prices of patented medicines are not excessive. Maintaining the top of TCC is more consistent with the mandate of non-excessiveness and has proven to be a successful method of keeping Canadian prices below the international median*[15].

[13] http://www.auditor.on.ca/en/content/annualreports/arreports/en17/v1_309en17.pdf Chapter 3 Section 3.09, Ministry of Health and Long-Term Care, Ontario Public Drug Programs (page 491)
[14] Figure 21; Annual Report 2017, Patented Medicine Prices Review Board (page 42)
[15] https://www.pmprb-cepmb.gc.ca/view.asp?ccid=1380

2. *Highest of TCC would be aligned with the Government's policy to reduce prices in Canada from the median of the PMPRB7 countries to the OECD median*[16]. Setting the maximum list prices (MLP) threshold by using the "the lower of 1. Median price of 11 comparator countries and 2. Highest price of the therapeutic class comparator (TCC)" would guarantee that the policy goal for prices to be at or below the median of the PMPRB 11 would always be met. However, a change from the highest of TCC to the median of the TCC would shift the balance and reduce prices even further towards the lowest priced comparator country (LIP), which is not stated as the policy intent.
3. *Highest of TCC would be aligned with the essence of the Board's voluntary compliance policy.* Using the median of TCC test is not a bright-line test. Patentees would systematically challenge the comparators in such a basket to obtain a more reasonable price. This would cause an unprecedented increase in resource use to settle disputes, investigations and hearings; much of which would be avoided by maintaining the bright-line highest of TCC test.
4. *Highest of TCC would be aligned with the vision of the Executive Director of PMPRB of a risk-based approach.* In the Modernization Paper of June 2016[17], the rationale stated for using a median TCC test is "to avoid upward drift in prices" of me-too drugs while having "less regulatory oversight of this class of drugs, not more. One solution to these competing considerations would be to introduce lower price ceilings for me-too drugs in the Guidelines at introduction but take a more relaxed approach to monitoring them on a go-forward basis. This approach would allow for more strategic and targeted use of the PMPRB's resources towards high-risk drugs while preserving the potential exercise of its jurisdiction over all patented medicines"[18]. A TCC test using the highest comparator would best reach this objective. Prices, as mentioned above, would always be below the median of PMPRB11 and other proposed Guidelines changes, such as reassessment and market size, would eliminate any "upward drift". Conversely, disputes arising from the proposed TCC test using the median would consume the PMPRB resources to be targeted at high-risk drugs.
5. *Highest of TCC would be aligned with encouraging competition:* Competition lowers prices in any marketplace. Knowing an innovative medicine would have its MLP set using the top of TCC provides the certainty to launch at least earlier than would otherwise be the case if the price was set at LIP because of a low median of dTCC. A price that more resembles MIP is more likely to lead to early launches of

[16] Amendments to the Patented Medicines Regulations: Cost-Benefit Analysis; Strategic Policy Branch - Health Canada; May 6, 2019 (page 42)
[17] PMPRB Guidelines Modernization - Discussion Paper; Patented Medicine Prices Review Board; June 2016 (page 18)
[18] ibid

products because it creates no international referencing issues. Consequently, additional competitors in the market provides more options for Canadian consumers and “purchasers” and lower price.

Demonstration examples have been prepared in Appendix B to elaborate the effects of using the median of TCC in evaluating the MLP for Category I and Category II medications.

Once again, the technical working groups could easily further clarify these recommendations for the PMPRB. Merck is completely aligned with the other members of the IMC in these recommendations. Merck has also included Appendix A, which provides further recommendations that seek to improve the Guidelines.

7. Conclusion

Clearly, one of the most problematic aspects of the Guidelines for Merck and the industry is the new economic factors and the way the PMPRB is proposing to apply them. The PMPRB has an unreasonably broad level of discretion to reassess a medicine and reapply the economic factors throughout the product life cycle, driving further pricing uncertainty, and this well beyond the excessive pricing standard, as reflected in the Patent Act.

If the PMPRB continues to proceed with the implementation of the Guidelines with the routine application of economic factors, Merck must explore all possible avenues to improve the Guidelines. Merck has outlined many practical challenges in complying with the Guidelines in their current form. Merck believes that the only way to work through these questions would be the implementation of technical working groups, particularly weighted on industry representatives that are responsible for the actual compliance activities and that have in-depth knowledge of the contracting environment in Canada.

While there are certainly many aspects to comment on the Guidelines, Merck has prioritized 1) transition provisions for grandfathered products, 2) a provision for a maximum reduction for the maximum rebated price (MRP) and 3) the use of the highest price of the domestic and international therapeutic class comparator (TCC) instead of the median in setting the MLP.

In this light, Merck is looking forward to continuing dialog with the PMPRB that aims to improve the translation of the regulations into operationally sound Guidelines, that provide high predictability of MLP and MRP for patentees during the launch phase, and that would result in increased launches and more timely access to innovative medicines for Canadian patients.

Appendix A – Other Suggested Changes to Improve Predictability and to Reduce Systematic Investigations and Enforcement

Merck has also prepared a list of other recommendations for the Guidelines that will help improve predictability that will reduce systematic investigations and enforcement:

1. Use of Lower of 1) Median of 11 Comparator Countries and 2) the Current Provincial List Price, for setting the MLP for products with a DIN prior to August 21st, 2019

   In section 59 of the proposed Guidelines, the PMPRB proposes that the MLP for all grandfathered patented medicines be set at the lower of (i) the MIP for the PMPRB11 countries or (ii) the Maximum Average Potential Price (MAPP) for the introductory period or the Non-Excessive Average Price (NEAP) for all subsequent periods. Using the MAPP or the NEAP in MLP setting is not an appropriate methodology as both of these thresholds may not be representative of the current list price of the product; especially in the case of the NEAP that could contain discounts, rebates and other benefits. Instead, Merck is recommending for PMPRB to use the current list price of a product as long as it is aligned to the product's introductory benchmark price (IBP) and any subsequent allowable increases taken by the patentee.

2. Status quo needed for reasonable relationship test

   One proposal of the draft PMPRB Guidelines is to change the reasonable relationship (RR) test: "the MLP or MRP of the new strength will be set to equivalent to the price per standard unit of the existing strength(s)[19]". The previous Guidelines allowed for cases of a new product of lower strength to be parity priced to the highest existing strength. The Guideline proposal of price per standard unit is flawed because the primary reason manufacturers launch line extensions is to meet an unmet need of special populations, such as pediatric and renal impairment patients, specifically for loading, titration, or reduction doses. Merck recommends keeping the reasonable relation test per the previous guidelines and allowing for flat pricing across formats.

   For example, assume an existing medicine is 100mg and sells for $1.00 per day and the patentee launches a pediatric dose of 25mg strength. Under the new Guidelines the maximum price would be $0.25 per day or -75% reduction. The patentee would perceive this price ceiling as "unreasonable" and, consequently, would not launch the product or dispute the price with the PMPRB. Equally, disputes arising from the

[19] PMPRB Guidelines 2019, Patented Medicine Prices Review Board (page 27)

proposed RR test would also consume PMPRB resources, again taking time and effort away from oversight on targeted high-risk drugs. From a balanced fairness perspective, the MLP set by PMPRB at -75% reduction would in most cases be significantly below the LIP; another flaw of these proposed Guidelines. Ultimately, the patient would be the one that would lose access to a required medicine.

3. ATC sub-level 4 for determination of comparators (no other option)

   As the innovation of new medicines would no longer be recognized by levels of therapeutic improvement; i.e. slight, moderate, substantial or breakthrough improvements, Merck is recommending that comparators for both the domestic and international TCC tests be solely based on the WHO ATC fourth sub-class level for the determination of comparators. If comparators do not exist, then only the MIP test would be conducted. This recommendation would provide a bright lines test for choosing comparators and would be create balanced fairness that would help reduce disputes in many areas, including the TCC tests as described above. Furthermore, Merck also recommends that the Human Drug Advisory Panel maintain its role in defining clinical comparators. Not using WHO ATC fourth sub-class level, could necessarily lead to inappropriate comparators that would drive down the dTCC and essentially default to LIP in almost every situation, which is inconsistent with the principle of maximizing Canada in the middle of the basket of 11 countries.

4. Status quo for determination of relevant indication (highest therapeutic advantage or market size)

   The PMPRB is proposing a change in their process of defining the Relevant indication. Merck is aligned with IMC that the methodology in the current PMPRB Guidelines for determining relevant indication is the most appropriate and efficient.

5. Complaints-based reassessments

   For the purpose of predictability and a more efficient use of resources, Merck is aligned with IMC recommendation that reassessments should be conducted primarily on the basis of exceptional circumstances (for example, on a complaints-only basis).

6. Market Size Based on Actual Net Sales

   The Guidelines are not clear on the application of market size. Whether used for classification or regulatory enforcement, Merck recommends that the market size factor should always be based on actual net revenues and not estimated ones. This method was confirmed on the PMPRB/Industry teleconference on January 17, 2020.

7. Create a Category Ia and Category Ib to distinguish between high cost and low cost/high use medications

   For simplicity, Merck has used the above nomenclature internally to help explain the difference between a product that enters Category I because of annual cost >=$25,000 (Category Ia), that would be evaluated for PEP and market size if total sales exceed $25 million. Contrarily, products that enter Category I because total sales exceed $25 million (Category Ib) would only be evaluated for market size. This helps clarify which economic factors will be applied on a Category I product.

8. Automatic classification of vaccines as Category II with specified use of dTCC

   Vaccines in Canada are predominantly managed by public health and subject to large tenders or contracts with PSPC or Sigma Santé. Jurisdictions determine specific public health budgets associated to expected vaccination rates. Overall, private market sales are minor in comparison with the public health markets. Contrary to medications that treat illnesses, there is a positive healthcare prevention impact between high usage and successful immunization of the Canadian population. Applying market size economic factor penalizes manufacturers for achieving a very important public health goal. Given the extremely low risk associated with excessive pricing in vaccines, Merck is recommending that all patented vaccines be regulated as Category II, without the application of economic factors and only using dTCC when there is an interchangeable vaccine as determined by National Advisory Committee on Immunization – e.g. MMR, Rotavirus, etc. Our recommendation is very much aligned with the BIOTECanada Vaccine Industry Committee (VIC).

9. Ability to reverse market size economic factor in the case of changing market conditions

   In the case where a market size economic factor is applied, there is currently a provision to increase the rate of reduction in MRP, but no provision to reverse the reduction of MRP in the case where the patentee suffers a reduction in total sales. In reference to the "balanced approach" principle, it would be more appropriate to allow for the reversal of part or all of the reduction of MRP in the case where total sales decrease. There are innumerable reasons for a manufacturer to suffer a reduction in sales, such as the increased competition in the market, an unfavorable product label update, a de-prioritization by the provinces, etc. Many of these factors are outside the control of the company and overly penalize us with a high reduction in MRP that further adds to the loss in sales in the market.

10. Elimination of Reporting Requirements Once Generic Competition Exists in the Canadian Market

    The proposed Guidelines look to reduce the reporting requirements for patented generic drugs. Merck recommends that the same complaint-based process be extended to patented medicines that experience loss of patent exclusivity in the market and face competition from multisource drugs that are interchangeable products. This recommendation would be aligned with the Modernization approach not to spend regulatory oversight on patented medicines that pose no risk of excessive pricing. This would be consistent with the principle of a balanced approach, i.e. treating patented generic multisource drugs and patented brand-name multisource drugs equally.

Appendix B – Examples of TCC Evaluations

In order to better illustrate the rationale for TCC test using the highest comparator medicine, Merck has prepared two examples, one for a Category I medicine and another for a Category II medicine.

Example 1 - Category I Medicine

Summary:

dTCC (highest)	$102
dTCC (median)	$70
MIP	$91
LIP	$74
Resulting final MLP	$74

dTCC variables:

Domestic Comparator 1	**Domestic Comparator 2**	**Domestic Comparator 3**	**Domestic Comparator 4**	**Domestic Comparator 5**
$102	**$95**	**$70**	**$68**	**$67**

PMPRB 11 Basket of International Comparators

Period	GER	FRA	SWE	ITA	UK	JPN	NE	BEL	NOR	SPN	AUS	MIP	LIP
1	100	100		95	91	100						100	91
2	100	100	95	95	91	100	92	90	80			95	80
3	100	80	95	95	91	93	92	85	80	85	80	91	80
4	100	80	95	95	91	93	92	80	80	80	74	91	74

Note: Prices are non-comparable based on reimbursement environment among PMPRB 11 countries (e.g. several countries do not enter into confidential agreements so the list price and list price erosion over time is tied to access, whereas PMPRB only regulates price without consideration of access in Canada).

For Category I medicines, the proposal by PMPRB to use a median of a TCC test would only intensify the uncertainty of estimating the MLP. Consequently, this would add to the delay of launching new innovative medicines in Canada, especially when the LIP is being set by a lowered priced country such as Australia that does not aspire to the same level of access to medicines as Canada. Patentees would now face ambiguity with both the calculation of MLP, which directly impacts MRP, with the latter already setting back the Canadian launch date for a new medicine in Canada due to the unpredictability of the PEP.

In the example above, let us assume that the patentee launches the new medicine at the end of period 4 at a list price of $90 based on the median of the PMPRB 11 test. The final

MLP, however, determined by the PMPRB is $74 and not $91 due to LIP, as the median of the dTCC test is $70; a 19% reduction. The patentee would likely dispute this final MLP, arguing that comparators 3,4 and 5 should not be included in the TCC basket. This would tie up resources at PMPRB.

Contrarily, maintaining the top of TCC test would offer much greater certainty in MLP for the patentee, and avoid these types of disputes while helping timely access to innovative medicines for patients. Notably, if the patentee believed in the pre-launch period that its new medicine would be subject to LIP, the company would probably choose to delay launch even further due to international price referencing.

In Category I medicines without a PEP, the patentee could choose to launch in Period 1 in Canada to benefit from the 5 countries/3-year rule. In the example above, the MLP, however, would still be less than the median of $100 at $91; a further 9% reduction, again due to LIP. Therefore, there would still be a significant revenue impact for the patentee. In this light of a median TCC, PMPRB is seen more as a price setter than a price regulator and patentees would systematically dispute the outcome.

Example 2 - Category II Products

As noted from the Modernization Discussion Paper, originally, the rationale for using the median of the TCC was to "avoid upward drift"[20] of Category II products.

To illustrate the rationale for the highest of TCC test – assume a launch of a new insomnia drug that provides moderate advantage, i.e. fewer side effects:

Summary:

dTCC (highest)	$1.37
dTCC (median)	$0.41
MIP	$1.30
LIP	$0.90
Resulting final MLP	$0.90

This example would be common for Category II medicines, especially those in a class with several competitors including generics. A median of TCC test has potential to set an MLP at "unreasonable" levels when compared to a product that are medically inferior. So, access to patients would be delayed due to unpredictability of MLP. Furthermore, with level of therapeutic advantage being removed as criteria for setting price ceilings, it is unclear how these medicines would be recognized for their moderate or substantial innovations. At least maintaining a top of TCC test would keep prices aligned with the most reasonable

[20] PMPRB Guidelines Modernization - Discussion Paper; Patented Medicine Prices Review Board; June 2016 (page 18)

relevant comparator; and prices would still be at non-excessive levels at or below the median of PMPRB 11.

In this example, the patentee would face a price decrease of -34% by using the median of the TCC. As mentioned above, there would be systematic challenges by patentees and PMPRB would be consuming more than its allocated share of resources on Category II medicines to resolve these disputes. This is contrary to a risk-based approached being proposed and to patients having more timely access to innovative medicines.

According to the PMPRB in past Outreach Programs, a large majority of medicines are not launched at the maximum average potential price (MAPP). As an example, PIFELTRO & DELSTRIGO, a fifth in class HIV medicines, launched in 2019 at a list price of approximately -25% below MAPP. This is attributed to the evolution of the pricing and reimbursement environment, i.e. competition; HTA agencies and the pCPA that ensure affordability of medicines. Maintaining a top of TCC test allows for the competitive aspects and the overall ecosystem to control list prices of Category II medicines with less enforcement by PMPRB, so the PMPRB can focus on innovative medicines that truly present a higher risk of excessive pricing.