Consultation on (Revised) PMPRB Guidelines
Takeda Canada Submission
August 4, 2020

Takeda Canada Inc. is making this submission in response to the request for submissions from the Government of Canada regarding the Patented Medicine Prices Review Board's (PMPRB) proposed Guidelines to accompany the newly amended *Patented Medicines Regulations.*

Executive Summary:

Takeda is responding to the latest proposed PMPRB Guidelines to express our disappointment that the revisions do not adequately address the concerns we expressed in our first submission to the PMPRB in February. We continue to fear that the guidelines will have a negative impact on Drugs for Rare Diseases (DRDs). Specifically, we believe:

- Applying new pricing guidelines to DRDs at this time is premature and should wait until after the federal government and the provinces have aligned on a rare disease strategy for Canada;

- Canada already trails behind other markets in patient access to DRDs and the proposed guidelines will only worsen this situation;

- The technical modifications in the revised guidelines will not prevent mechanisms like Therapeutic Criteria Levels (TCL) and pharmacoeconomic value calculation from disproportionately impacting DRDs.

Takeda Canada is convinced that despite the modest changes made to revise the guidelines this spring, the proposed reforms under consideration will severely damage an already-fragile Canadian market for DRDs – a view we share with healthcare professionals and patient groups.

Rather than waiting for the outcome of any challenge to the recent ruling by the Federal Court on the legitimacy of the Maximum Rebated Price (MRP) concept, the Board would be better served by suspending the current consultation, establishing technical working groups that leverage the expertise of patentees, and re-releasing a revised Guidelines package that is consistent with regulatory tools within its mandate.

Takeda would welcome the opportunity to help the Board develop an alternative approach to pricing and access for DRDs, which represent the most fragile aspect of the Canadian pharmaceutical market. We remain willing to lend our knowledge of global best practices to design innovative and inclusive solutions.

Legal Disclaimer:

This submission and any other engagement in consultations with the PMPRB regarding the Patented Medicines Regulations, as amended, and related Draft Guidelines are without prejudice and are not intended and should not be interpreted as supporting the amendments to the PMPRB Regulations or Draft Guidelines. Takeda continues to have concerns about the legality of the Patented Medicines Regulations, as amended, which are the subject of an ongoing legal challenge. Takeda reserves its full legal rights to oppose any aspect of the Patented Medicines Regulations and related Guidelines.

Takeda Has a Unique Commitment to Developing Drugs for Rare Diseases (DRDs)

Takeda is one of the world's oldest and fastest growing pharmaceutical companies. Founded in Japan in 1781, we now operate in more than 80 countries around the world, including Canada. More than a decade ago, Takeda made the strategic decision to become a specialty biologics company and today we have a deep and sustained commitment to developing DRDs. Forty percent of our marketed products are drugs for rare diseases and more than 50% of our pipeline products have an orphan drug designation (as per the U.S. FDA and EU EMA definitions of orphan drugs).

Takeda's commitment to supporting patients living with rare diseases is underscored by our role as co-chair of the *Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease*, alongside EURORDIS and Microsoft.[1] The Global Commission is a unique and transformative international alliance of clinicians-scientists, patient groups and industry leaders committed to making a major difference in the lives of millions of children and their families by implementing an actionable roadmap to shorten the multi-year journey that so many patients endure before they can obtain the accurate diagnosis required to unlock a potential treatment path.

It is through this unique lens that Takeda is viewing our submission to the PMPRB, outlining our concerns and recommendations about the current reform process and its potential impact on patients with rare diseases. Takeda is a proud member of both Innovative Medicines Canada and BIOTECanada, and we support the submissions that both associations have delivered to the Board as part of this consultation process. However, we also believe that our rare disease focus, our understanding of other global markets and our experience in bringing drugs for rare diseases to patients makes Takeda uniquely positioned to share our own response to the proposed regulatory changes under consideration.

Takeda Continues to Have Three Fundamental Concerns with the PMPRB's Proposed Reforms

First, we believe that the reforms will confuse and complicate parallel government efforts to fight rare diseases. These efforts include the Government of Canada's commitment to developing a national strategy for DRDs – anchored by $1B in new funding over two years starting in 2022-23 and continuing with up to $500M per year[2] – multiple pan-Canadian and provincial efforts, including the Care4Rare project that leverages research organizations across Quebec, Ontario, Alberta and British Columbia, as well as federal organizations such as the Canadian Institute for Health Research and Genome Canada.

[1] www.globalrarediseasecommission.com/

[2] Government of Canada. https://www.budget.gc.ca/2019/docs/plan/budget-2019-en.pdf

As the Board may know, the Provincial/Territorial Expensive Drugs for Rare Diseases Working Group has also played a major role in advancing a pan-Canadian DRD policy agenda. Participating Ministers of Health supported in principle the stated goal to *"implement a proactive, consistent, fair and transparent process to assess complex/specialized drugs for the purpose of making responsive funding decisions."*[3] This promising example of interjurisdictional collaboration is exactly the kind of initiative that should be launched and reviewed before a new pricing regime for DRDs comes into effect.

Given the number and variety of existing initiatives, projects and proposals focused on improving the treatment of patients with rare diseases, it is critical that the PMPRB ensure that its reform efforts don't undermine or destabilize a critical mass of nascent and dynamic efforts. For this reason, Takeda believes it is premature to apply new pricing guidelines to DRDs before the federal government and the provinces have aligned on a rare disease strategy for Canada, in order to maximize strategic alignment and minimize inadvertent contradiction.

Second, we are convinced that the reforms will make Canada even more of an outlier in the treatment of DRDs compared to its global peers. Contrary to the PMPRB's assertion that its changes would bring Canada closer to its peers in how it determines the prices paid for new medicines, the Board's proposed regulatory reforms would actually leave Canada behind countries like France, the Netherlands and Switzerland, which all have fast-track mechanisms for access/reimbursement for DRDs.[4]

Based on recent research[5] from the Office of Health Economics (OHE), Canada sits well behind its global peers in terms of the number of DRDs (known as Orphan Medicinal Products or OMPs in Europe) that receive public listing and the length of time it takes for these DRDs to get listed. Of the 16 countries assessed, Canada sits 11th with a rate of reimbursement of DRDs/OMPs of just 36.2%. This places Canada in front of three eastern European and two Nordic countries but well behind the leading nations of Germany, the Netherlands and France as well as other G7 markets such as the United Kingdom and Italy. Since the study uses Ontario market access data as a proxy for Canada – and the country's largest province tends to reimburse more DRDs than smaller provinces – Canada's true access environment may be even worse.

[3] http://www.raredisorders.ca/content/uploads/EDRD-supplemental-process-background_24Oct2018_Final.pdf

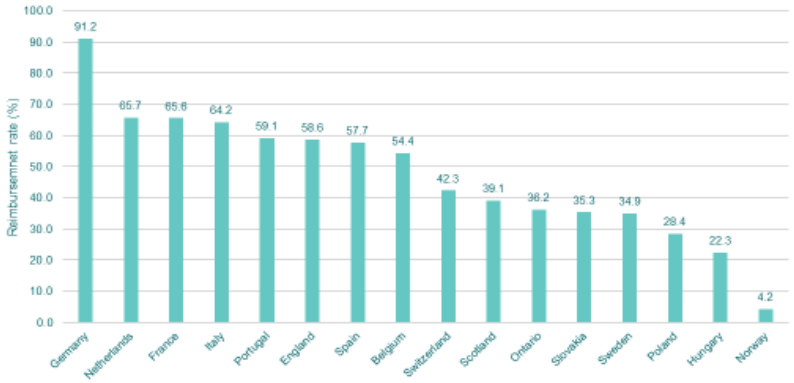
[4] Short H, Stafinski T, Menon D. A National Approach to Reimbursement Decision-Making on Drugs for Rare Diseases in Canada? Insights from Across the Ponds. Health Policy. 2015;10(4):24-46.

[5] Office of Health Economics (OHE). Comparing Orphan Medicine Reimbursement in Europe and Canada. Expected publication date August 2020.

Rate of reimbursement of OMPs

Reimbursement rates by country i.e. count of indications with reimbursement status out of the full list of authorised OMPs from 2000 to 2019 (%)

- The country providing the highest level of coverage to OMPs is Germany (with over 90%), followed by the Netherlands, France and Italy (with around 65%)
- The three countries with the lowest level of coverage are Poland, Hungary and Norway (below 30%)



At a time when improving access to DRDs needs to be made a priority, we fear that the proposed guidelines will only serve to further delay broad and timely access to DRDs in Canada. This would be especially unfortunate given recent moves by the Canadian Agency for Drugs and Technologies in Health (CADTH) to consider different willingness-to-pay thresholds for both DRDs and many cancer therapies – a more flexible, nuanced and compassionate approach to DRDs that aligns with many of Canada's global peers.

Third, despite some recent revisions to the proposed regulatory reforms, we believe that the technical modifications outlined by the Board are insufficient to address a set of fundamental flaws that will disproportionately impact DRDs. We agree with IMC that the new economic factors and the Maximum Rebated Price (MRP) concept will negatively impact the launch of many DRDs in Canada.

More specifically, we also strongly believe that the introduction of a newly proposed scientific review process that identifies Therapeutic Criteria Levels (TLC) creates clinical evidence threshold requirements that are biased against DRDs. By their very nature, clinical trials for DRDs are generally comprised of smaller patient populations and for ethical reasons do not include a Phase 3 or a head-to-head study. These clinical studies are designed to address immediate unmet needs related to patients' quality of life, and to provide new alternatives to patients with few if any treatments.

A review of rare disease pipeline products on clinicaltrials.gov, leads one to conclude that based on trial design, patient numbers and data gaps, the vast majority of new DRDs would never be designated above Level 4 under the proposed guidelines. Level 4 category drugs are automatically subject to a 50% price reduction, which creates a huge disincentive for companies to introduce any drug in Canada as part of a first global launch wave. Like all stakeholders with a specific focus on rare disease, Takeda is gravely concerned that the Board's categorization methodology will reduce the therapeutic options available to

many of the most vulnerable and marginalized patients. It's not clear whether this is intended or based on a lack of understanding of the rare disease environment. In either case, this is unacceptable to Takeda.

Furthermore, we believe pharmacoeconomic (PE) value calculations are unreliable instruments whose heavy dependence on assumptions gives them significant variability. It is for this reason the PE calculations are typically used as a data point for reimbursement negotiations, not as a reasonable and appropriate tool to establish manufacturer net prices. In fact, using pharmacoeconomic factor to establish a net price ceiling will itself create significant uncertainty in product launch calculations, especially since including both market size and a cumulative factor in future pharmacoeconomic evaluation could lead to PMPRB-mandated list price reductions of 67.5% on DRDs. (On this note, the OHE just released a report that identifies critical limitations in using pharmacoeconomics to regulate the prices of new medicines, arguing that all too often this approach ignores the real bargaining power of payers, the real sunk costs of research and development, the behaviour of other developers and the dynamic nature of healthcare budgets.[6])

PMPRB's Proposed Changes Will Further Weaken an Already Fragile Market for DRDs

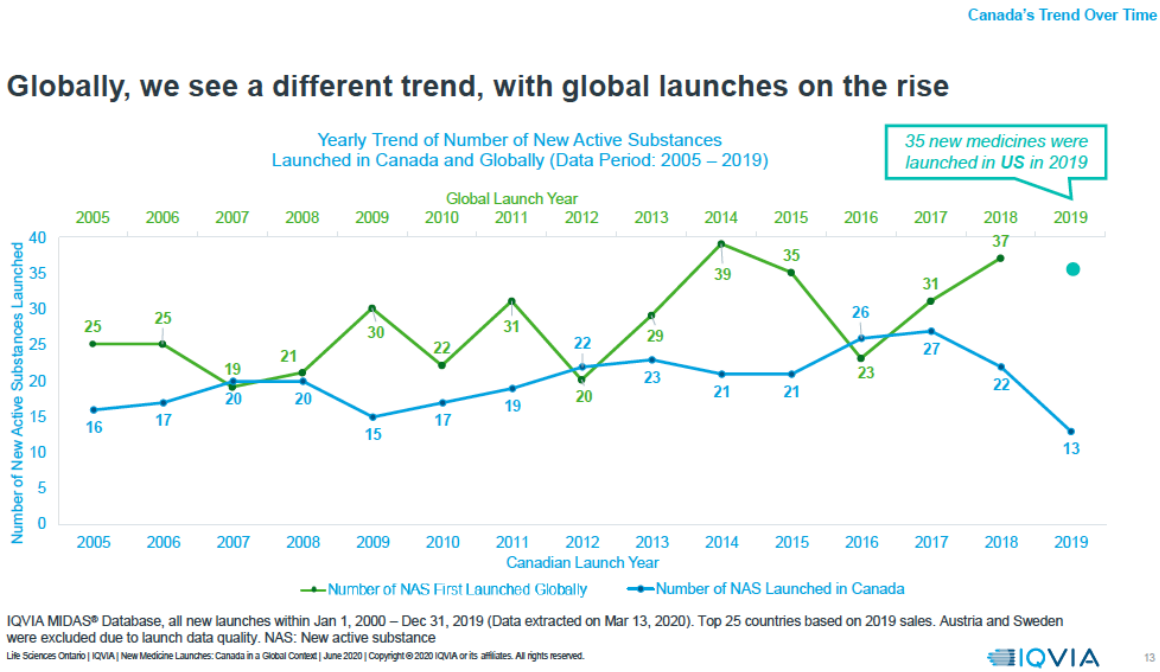
At the core of Takeda's concerns is our fear that the new pricing regime being proposed by the Board will introduce significant additional uncertainty into what is already a risky, slow and expensive process. In fact, Canada's declining attractiveness as a destination for new medicines is already being felt**.** On June 22nd, Life Sciences Ontario published a study by the global consulting firm IQVIA entitled *New Medicine Launches: Canada in a Global Context*.[7] The purpose of the study was to answer two core questions: (1) How does Canada compare to international markets in terms of time to launch, proportion of launches and sequence in launch for new medicines?; and (2) Have there been changes in Canada since recent federal policy announcements?

IQVIA's analysis covered the period from 2000 to 2019 and encompassed the top 25 countries around the world by pharmaceutical sales. The resulting report generated two key conclusions. First, across the full 20 years of the survey, Canada was on average the 4th fastest to launch a new active substance – just behind the US, Germany and the UK. Second, Canada ranked 9th based on the proportion of new medicines launched globally. The country saw 66% of new active substances (NAS) launched in the last 20 years, behind the US with 89%.

[6] https://www.ohe.org/publications/bargaining-approach-theory-icer-pricing-and-optimal-level-cost-effectiveness-threshold

[7] Life sciences Ontario, IQVIA, New Medicine Launches: Canada in a Global Context. June 2020.

Unfortunately, the positive environment initially outlined by IQVIA over the early years of the study period is contradicted by the data from the last two years. After reaching an all-time high of 27 NAS launches in 2017 (vs. 31 first launched globally), the gap between Canada and other markets has begun to grow significantly. Canada saw only 22 NAS launches in 2018 (vs. 37 globally) and 13 in 2019 (vs. 35 in the US alone.) In 2018, 21 out of 37 NAS launched globally were not launched in Canada – and of those 21 medicines, six were DRDs.



Rare Disease Patients, Healthcare Providers and Researchers Echo Our Concerns

Unfortunately, a lot of the public discourse on the guidelines tends to be focused on numbers and not people. It's important to remember that, for good or for bad, these types of policy changes have the potential to significantly impact people's lives. That's why it's so important that we work collaboratively to ensure we get it right. Here's what Canadians living with rare diseases and those who care for them and represent them are saying:

"The diagnostic odyssey for a Fabry patient averages 7-10 years for a proper diagnosis. So much time has already been spent and that time is incredibly precious as disease progression can occur quickly. Patients can't afford to lose more time and we should not be putting in place guidelines that further delay patients from receiving therapies. Let's focus on ways to improve this."

-Julia Alton, Executive Director, Canadian Fabry Association

"The patient is at the center of what we do; we all strive to give the best possible care to our patients whether that be through a licensed drug or enrolling a patient into a clinical trial. If these guidelines are approved the ability to access these groundbreaking and life changing therapies will be greatly diminished. The impact will not only be felt by the patient, but it will also impact the strained health care system."

- Kaye LeMoine, RN CCRP, National Program Manager, Canadian Fabry Disease Initiative

"The process to go through for the approval of treatments for rare disorders in Canada is long and difficult. It is also very complicated and as such, it is very difficult for a small organization such as MPS Canada to determine what the impacts of this policy change will be. We hope this reform will not create further delays and restrict the access to treatment and research for Canadians in the future. We understand this process creates great uncertainty for all key stakeholders, patients included, and continue to inform ourselves on the evolving situation."

-Melissa Bilodeau, Chair of the Canadian MPS Society

As mentioned previously, through the Global Commission Takeda is working with patient organizations, clinicians-scientists and technology leaders to reduce the average length of time it takes to accurately diagnose a rare disease. Researchers and clinicians are also working hard to develop, trial and bring to market new drugs for rare diseases to patients who desperately need them. From our discussions with our partners and collaborators, it's clear that there is a broad sense that recent gains made in these areas will be lost if the PMPRB's reforms come into effect as currently proposed. Nobody stands to gain if this happens. Least of all patients.

Beyond our Core Concerns, Takeda is Urging a Revitalized Approach to Industry Engagement

As a party to the legal action launched by IMC and several of its member companies in 2019, Takeda welcomed the June 29, 2020 finding by Justice Manson of the Federal Court of Canada that the new price calculations in the newly amended *Patented Medicines Regulations* were invalid, void, and of no force and effect. This calls into question the validity of the MRP concept that serves as a cornerstone of the package of proposed regulatory reforms.

Rather than waiting for the outcome of any challenge to the ruling by the Federal Court, the Board would be better served by temporarily suspending the current consultation, establishing technical working groups that leverage the expertise of patentees, and re-releasing a revised Guidelines package that is consistent with regulatory tools within its mandate.

Takeda would welcome the opportunity to help the Board develop an alternative approach to pricing and access for DRDs, along with other high-value products like plasma products and vaccines – the latter a pivotal component of Canada's response to the COVID-19 pandemic.

We believe that DRDs represent the most fragile aspect of the Canadian pharmaceutical market, and we remain willing to not only clarify and elaborate on the challenges around the corner, but also lend our knowledge of global best practices to the Board as it works to design a set of innovative and inclusive solutions.

As a company that has invested more than $1B in innovation partnerships in Canada in recent years, Takeda understands that one of the things that makes the country an attractive place to invest is the reputation, the quality and the openness of its world-class research centres and the researchers they support. **By addressing the concerns outlined above and revising its proposed regulatory approach, the PMPRB can ensure that Canada remains an attractive market to invest in promising basic and applied research, commercialize promising new technologies and bring innovative medicines to patients.**