Better Health, Brighter Future

Consultation on PMPRB Guidelines
Takeda Canada Submission

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 Canada brings a unique perspective to our analysis of the proposed reforms, as a company with a major commitment to patients living with rare diseases. Although we believe we share with the PMPRB a broad and unifying goal of sustaining a vibrant Canadian market for drugs for rare diseases (DRDs), we are also concerned that the changes being proposed will confuse and complicate other pan-Canadian efforts currently underway aimed at improving patient access to DRDs, make Canada an outlier compared to how other countries with comparable healthcare systems price and reimburse DRDs, and undermine the attractiveness of Canada as a destination for global research and development and for launching new products. Based on the core concerns noted above and outlined over the following pages, Takeda recommends that the PMPRB delay implementing a new pricing framework as it applies to DRDs and commit to working with partners in industry and beyond to more carefully assess the impact of its reforms.

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.

Introduction

Across Canada, the emergence of many new drugs for rare diseases (DRDs) is an exceptional success story, one that is filled with countless examples of patients with rare diseases whose lives have been transformed by life-altering medicines.

The quest to discover, develop and deliver new drugs for rare diseases is already a long, risky, complex, and costly one. Unfortunately, proposed regulatory reforms to the Patented Medicine Prices Review Board (PMPRB) have the potential to weaken an already-arduous process.

As a company with a major commitment to helping patients suffering from rare diseases, Takeda Canada brings a unique lens to our analysis of the proposed reforms – a lens that has illuminated three fundamental concerns.

First, there are currently many moving pieces surrounding and shaping DRD policy – in particular, both the commitment from the Government of Canada to develop a new strategy for DRDs, and a new Supplemental Review Process emerging from sustained and successful collaboration between provinces and territories.

Second, the proposed regulatory reforms would make us an outlier compared to how peer countries reimburse DRDs. Whereas, the experience of other comparator jurisdictions shows the value of developing tailored and modified pricing and reimbursement frameworks for these medicines.

Finally, we fear the impact of the proposed changes will not only undermine the attractiveness of Canada as a destination for global research and development (R&D investment) but also discourage companies from bringing innovative new treatments to the Canadian market. By many estimates Canada is already falling behind other countries in terms of timely access to life- altering medicines. If these changes are implemented as is, they will leave Canadians with rare diseases significantly disadvantaged compared to their peers in other developed economies.

Based on these concerns – and supported by our experience with an exceptionally broad array of global pricing regimes – Takeda Canada is respectfully calling on the Board to delay the implementation of a new pricing framework, particularly as it applies to DRDs, and commit to working with partners in industry and beyond to more carefully assess the impact of its reforms on the most fragile aspect of the Canadian pharmaceutical market.

Takeda Has a Unique Commitment to Developing Treatments for Rare Diseases

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.

For the first 200 years of our history, Takeda focused its research and development efforts on primary medicine. However, more than a decade ago we 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). **It is through this unique lens that Takeda is viewing our submission to the PMPRB, outlining our views, our concerns and our recommendations about the current reform process and its potential impact on patients with rare diseases.**

Although Takeda entered the Canadian market in 2009 – more than 20 years after the previous PMPRB regulations went into effect – we have spent the past decade making significant R&D investments across the country. As of January 2020, Takeda Canada has either invested or committed over $1.3 Billion CAD through grants, donations, and investments in clinical research and scientific partnerships. Takeda has an increasing commitment to research in Canada, including our announcement at the end of 2019 that we are investing $1 Billion US in a partnership with the Canadian company Turnstone Biologics to develop novel viral immunotherapies, and more recently, our investment of $2.4 million CAD in the first collaborative Canadian lung cancer research project with Princess Margaret Cancer Centre. **These investments demonstrate our commitment to research and development and to commercializing transformative discoveries from Canada's world-class scientists.**

There are Multiple Challenges to Discovering New DRDs

Health Canada has defined rare diseases as *"life-threatening, debilitating or serious, and chronic conditions affecting a small number of patients."*[1] Although each of these diseases affects a small number of patients, their collective reach is significant, with approximately 2-3 million Canadians suffering from one or more of the approximately 7000 rare diseases identified to date.[2,3] Estimates indicate that 350 million people worldwide – or 5% of the world's population – are affected by one of these rare diseases.

Eighty percent of rare diseases are genetic, which means children are particularly impacted. In fact, 50% of rare diseases will begin in childhood and 30% of children with a rare disease will not live to see their 5th birthday. In the U.S. and UK, the average time to correctly diagnosis is 5-7 years, requiring visits to eight specialists, and 40% of patients are misdiagnosed at least once.[4] Even once properly diagnosed, there is the risk that a treatment will not exist. **Of the 7000 known rare diseases, only 6% have an available treatment – making individuals with rare diseases among the most disadvantaged and at-risk patients in the world.[5]**

The impact of rare diseases is exacerbated by the challenges facing those searching for a cure. By their very nature, most rare diseases are under-researched, and therefore require a greater amount of time before their underlying biology and pathophysiology can be understood. Clinical trials often take longer for the same reason and require more sites in more countries to ensure a critical mass of patient participants. For these and other reasons, the success rate of bringing rare disease drugs to market is low.

For our part, Takeda has adopted a distinctive approach to addressing and mitigating these challenges. Adopting a strong focus on a research and development (R&D) partnership model, Takeda has made sustained investments in the world's leading life sciences clusters – including multiple locations in Canada. Takeda's investments in DRDs is also not limited to product development and commercialization. Together with Microsoft and EURORDIS, we are a founding member of the *Global Commission to End the Diagnostic Odyssey for Children with Rare Diseases.* The Global Commission has developed a roadmap with actionable recommendations to help end the multi-year diagnostic odyssey that afflicts too many children with a rare disease.

With so many factors impeding the process of bringing rare disease products to market, Takeda believes that the only way forward involves government, industry and patient organizations working together, not only to reduce current challenges but also to prevent the emergence of new

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[1] Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment. Report of the Standing Committee on Health.
https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf

[2] Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment. Report of the Standing Committee on Health.
https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf

[3] Health Canada. About drugs and rare diseases in Canada.
https://www.canada.ca/en/health-canada/services/licences-authorizations-registrations-drug-health-products/regulatory-approach-drugs-rare-diseases/about-drugs-rare-diseases.html

[4] Rare Diseases Impact Report: insights from patients and the medical community 2013. Global Genes. Global Genes fact sheet on rare diseases @ https://globalgenes.org/rare-diseases-facts-statistics/;

[5] Canadians Affected by Rare Diseases and Disorders: Improving Access to Treatment. Report of the Standing Committee on Health.
https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf

hurdles. **This fundamental belief underpins our concerns about the PMPRB reform process, which we believe will delay, distract and discourage the efforts of companies to bring new DRDs to Canadian patients.**

Our concerns cluster around three fundamental arguments

1. **The Reforms Will Confuse and Complicate Parallel Government Efforts to Fight Rare Diseases**
2. **The Reforms Will Make Canada an Outlier in the Treatment of DRDs Compared to its Global Peers**
3. **The New Pricing Regime Will Introduce Significant Additional Uncertainty into What is Already a Risky, Slow and Expensive Process for DRDs**

1. The Reforms Will Confuse and Complicate Parallel Government Efforts to Fight Rare Diseases

In the federal budget released in March 2019, the Government of Canada announced its plans to work with partners to develop a national strategy for DRDs, with the eventual goal of providing patients with rare diseases better and more consistent coverage for their treatments. The strategy will establish a coordinated plan for gathering and evaluating evidence for drugs for rare diseases, improve the consistency of decision-making and access across the country, and negotiate prices with drug manufacturers.[6] **Along with the announcement of a strategy, the government also committed new funding to help Canadians with rare diseases, beginning with $1B over two years in 2022-23 and continuing with up to $500M per year on an ongoing basis.**

Complementing this strategy, Health Canada has been working on new processes for the management of drugs for rare diseases under its Regulatory Review of Drugs and Devices (R2D2) initiative – a major reform initiative designed to streamline and simplify those regulatory pathways most in need of modernization.[7]

Alongside these cornerstone rare disease initiatives, the government has also funded several projects to help address specific issues with rare diseases – many of which require (and support) extensive provincial collaboration. The Care4Rare project is a pan-Canadian initiative involving 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.

Provinces have also been asking the federal government to address issues with rare diseases. Speaking about a potential area of focus for a National Pharmacare program, Ontario's Minister of Health the Hon. Christine Elliott told the media in December 2019 that *"I think that we should start with where we see a real problem, and Ontario sees a real problem with the rare and orphan disease drugs."*[8] Ministers of Health in other provinces have made similar requests that the federal government address these issues.

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

[7] Health Canada's role – Drugs for rare disease. CADTH Symposium 2019. https://cadth.ca/sites/default/files/symp-2019/presentations/april15-2019/A1-presentation-mbettle.pdf

[8] Ontario focused on rare disease drugs ahead of national drug plan talks. https://www.reuters.com/article/us-canada-pharmaceuticals-ontario/ontario-focused-on-rare-disease-drugs-ahead-of-national-drug-plan-talks-idUSKBN1Y62EZ

Collectively, the provinces have been working through the Provincial/Territorial Expensive Drugs for Rare Diseases (EDRD) Working Group. This group proposed a Supplemental Review Process, with the stated objective to *"implement a proactive, consistent, fair and transparent process to assess complex/specialized drugs for the purpose of making responsive funding decisions."*[9] The proposal was supported in principle by the Provincial/Territorial Health Ministers, with stakeholder consultations wrapping up in early 2019. 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.

Taken together, these initiatives, projects and proposals demonstrate both the determination of multiple stakeholders to improve the treatment of patients with rare diseases and also the need to ensure that the PMPRB's reform efforts don't undermine or destabilize a critical mass of nascent and dynamic efforts.

2. The Reforms Will Make Canada an Outlier in the Treatment of DRDs Compared to its Global Peers

The PMPRB has indicated that Canada is currently an outlier among other nations in that it does not use health technology assessments, budget impact assessments, or actual market prices as factors in determining the prices paid for new medicines. However, that is simply not true when we compare Canada to how other countries manage reimbursement of DRDs.

While many of the countries identified by the PMPRB use some measure of value to determine reimbursement for most drugs (generally an incremental cost-effectiveness ratio), when it comes to DRDs the use of value assessments is far more nuanced. In fact, as the following table demonstrates, in some cases cost-effectiveness is used occasionally, in a consultative manner, or simply not at all.

Use of Cost-Effectiveness Measures in Regulating Price and Reimbursement of DRDs

Country	**Use of Cost-Effectiveness Measurements**	**Notes Specific to Drugs for Rare Diseases**
Belgium	No	Cost-effectiveness analysis is not required as part of a reimbursement submission for drugs for rare diseases.[10,11]
France	Consultatively	Cost-effectiveness analysis is used in a consultative way in price negotiations in the reimbursement process but is not directly tied to price. If yearly sales are < €20 million (including taxes) in the second full year, cost-effectiveness is not used.[12]

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

[10] Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. Policies for Orphan Diseases and Orphan Drugs. KCE reports 112C [Internet]. Brussels: Federaal Kenniscentrum voor de gezondheidszorg - Centre fédéral d'expertise des soins de santé – Belgian Health Care Knowlegde Centre; 2009 [cited: 2020 Jan 23]. Available from: https://ec.europa.eu/health/ph_threats/non_com/docs/policies_orphan_en.pdf.

[11] Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet Journal of Rare Diseases. 2011;6(1):42.

[12] Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. Eur J Health Econ. 2018;19(1):123-52.

Japan	Occasionally	Cost-effectiveness is not routinely used to determine the prices of drugs as part of the reimbursement process for rare diseases, though a cost-effectiveness analysis may be requested if deemed necessary.[13]
Netherlands	Occasionally	DRDs are not required to submit a cost-effectiveness analysis when limited data are available. For DRDs used in hospital, access is allowed with evidence generation and a reassessment in 3-7 years.[14]
Australia	Occasionally	A cost-effectiveness analysis is required to be submitted to the Pharmaceutical Benefits Advisory Committee, but cost-effectiveness is not considered in reimbursement decisions if a drug qualifies for the Life Saving Drugs Program.[15]
UK	Partially	Reimbursement authorities consider cost-effectiveness and budget impact, but special consideration is given to drugs for ultra-rare diseases.[16,17,18]

As the previous analysis makes clear, there are several countries who either do not use cost-effectiveness when making reimbursement recommendations about DRDs or have adopted alternate means of access and/or assessment (e.g. coverage with evidence generation or assessments that focus on clinical benefit and/or the affordability).

Even the countries that do use cost-effectiveness estimates to assess value and determine the price and reimbursement of DRDs – including Italy, Sweden and Norway – acknowledge the increased uncertainty in measurements of clinical benefit in rare diseases and accept a higher willingness-to-pay threshold for DRDs than for other drugs.[19,20] Many comparator countries also make other efforts to help DRDs reach patients faster: France, the Netherlands and Switzerland all have fast-track mechanisms for access/reimbursement for DRDs.[21]

[13] Kogushi K, Ogawa T, Ikeda S. An impact analysis of the implementation of health technology assessment for new treatment of orphan diseases in Japan. Expert Review of Pharmacoeconomics & Outcomes Research. 2019:1-17.

[14] Czech M, Baran-Kooiker A, Holownia-Voloskova M, Kooiker C, Sykut-Cegielska J. Bridging East with West of Europe - a comparison of orphan drugs policies in Poland, Russia and The Netherlands. Acta Poloniae Pharmaceutica - Drug Research. 2018;75(6):1409-22.

[15] Australian Government Department of Health. New medicine applications for the life-saving drugs program. Commonwealth of Australia [Internet]. [Cited 2020 Jan 24]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/lsdp-applications.

[16] Denis A et al., op cit.

[17] NICE. Changes to NICE drug appraisals: what you need to know. National Institute for Health and Care Excellence [Internet]. 2017 Apr 4 [cited 2020 Jan 24]. Available from: https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know.

[18] Tordrup D, Tzouma V, P K. Orphan drug considerations in health technology assessment in eight European countries. Rare Diseases and Orphan Drugs. 2014;1(3):83-97.

[19] Ibid.

[20] Statens legemiddelverk. Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. Statens legemiddelverk (Norwegian Medicines Agency) [Internet]. [Cited 2020 Jan 25]. Available from: https://legemiddelverket.no/Documents/English/Public%20funding%20and%20pricing/Documentation%20for%20STA/Guidelines%20151018.pdf.

[21] 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. Healthc Policy. 2015;10(4):24-46.

In Canada, public agencies have shown their willingness to accept a separate process and a different willingness-to-pay threshold for certain drugs – including recent Canadian Agency for Drugs and Technologies in Health (CADTH)'s Common Drug Review (CDR) reviews of DRDs and many of the cancer therapies reviewed and assessed by the pan-Canadian Oncology Drug Review (pCODR). While the pCODR Expert Review Committee's deliberative framework includes cost-effectiveness, it is but one component in a decision-making process that also takes into consideration the overall clinical benefit, alignment with patient values and the feasibility of adoption into the health system. The framework clearly states that "…no single element over-rides another, but rather that pERC uses the sum of all elements to formulate a funding recommendation."[22]

As a result, Canada should be commended for currently having HTA and reimbursement processes that allow for more a flexible and nuanced approach to DRDs – a compassionate compromise that aligns with many of its global peers. Rather than being thrown out, this process should be protected or extended, or one of the most important Canadian drivers of DRD discovery and development will be eliminated.

3. The New Pricing Regime Will Introduce Significant Additional Uncertainty into What is Already a Risky, Slow and Expensive Process

Takeda Canada is a member of both Innovative Medicines Canada and BIOTECanada. Both associations have spelled out their issues with the PMPRB's proposed new pricing framework in great detail and Takeda shares their concerns. The purpose of our submission is to complement their efforts and their arguments through our own DRD-based analysis.

There are currently no treatments for 94% of the rare diseases identified, highlighting the need to ensure that Canada and other developed economies continue to identify, sustain and strengthen incentives to encourage the development of new DRDs. [23] **Rather than supporting the acceleration and expansion of access to DRDs, however, the PMPRB's proposed reforms are likely to harm the investment ecosystem that supports research, innovation and commercialization across Canada.**

Takeda believes that the PMPRB draft guidelines contain four specific challenges for DRDs:

- **Using a pharmacoeconomic factor to establish a net price ceiling ignores the difficulty of evaluating the cost-effectiveness of a DRD through economic modelling.** Many products used to treat rare disease have complicated epidemiology, an absence of comparable alternatives, and high treatment costs due to low patient population. For all of these reasons, the "one-size-fits-all" incremental cost-effectiveness ratio (ICER) value framework does not factor in the unmet need of a patient suffering from a rare disease for which there are few if any available treatment options.

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[22] Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian Oncology Drug Review (pCODR). pCODR Expert Review Committee Deliberative Framework. CADTH [Internet]. 2016 Mar [cited 2020 Feb 11]. Available from: https://www.cadth.ca/sites/defaut/files/pcodr/The%20pCODR%Expert%20Review%20Committee%20%28pERC%29/pcodr_perc_deliberative_frame.pdf

[23] Canadian's Affected by Rare Diseases and Disorders: Improving Access to Treatment. Report of the Standing Committee on Health. https://www.ourcommons.ca/Content/Committee/421/HESA/Reports/RP10349306/hesarp22/hesarp22-e.pdf

- **Including both market size and a cumulative factor in future pharmacoeconomic evaluation means there is no protection for net price reduction.** This could potentially lead to the PMPRB effectively mandating net price reductions greater than 80%[24] on DRDs and potentially lower than the PMPRB's basket of 11 countries – a scenario that would make new product launches virtually impossible.

- **The specific reference to rare diseases in the market size factor section of the draft guidelines is insufficient to reflect the unique market dynamics of DRDs.** The proposed additional factor of +50% of Pharmacoeconomic Price (PEP) for drugs for rare diseases will only apply to the initial $12.5M of annual revenues, after which DRDs will be evaluated the same as other medicines. This additional factor will therefore do little to assist access to DRDs.

- **The need for constant monitoring and year-over-year reassessment will inject considerable unpredictability into the lifecycle of DRDs.** The complexity and regulatory burden of the draft guidelines will make it difficult for the companies developing these medicines to comply, given the fact that so many firms focusing on DRDs are small biotechs with extremely limited, high-risk pipelines.

Based on the four factors outlined above, Takeda believes that attracting new investment to support Canadian clinical research will become an uphill battle. Uncertainty about the pricing for new DRDs will raise questions about the ethics of conducting clinical trials for investigational therapies in Canada, if there is no viable pathway for them to continue that therapy once the clinical trial has ended.

The Board's proposed reforms, then, generate two related risks. First, attracting R&D investment into the country's biomedical sector will become increasingly difficult. Second, there will be a significant delay in the timing of new treatments for Canadians suffering from rare diseases as Canada becomes a less attractive market for new innovations.

Granting an Implementation Delay for DRDs is Imperative

Takeda believes that we share with the PMPRB a broad and unifying goal of sustaining a vibrant DRD market in Canada. Where we diverge is in our assessment of *how* best to achieve that goal.

Based on the three core concerns outlined over the preceding pages, Takeda recommends that the PMPRB delay implementing a new pricing framework as it applies to DRDs and commit to working with partners in industry and beyond to more carefully assess the impact of its reforms on the most fragile aspect of the Canadian pharmaceutical market. We would be pleased to facilitate, sponsor or participate in a multi-stakeholder roundtable or working group to clarify and elaborate on the challenges around the corner – and to lend our knowledge of global best practices to the design of innovative and inclusive solutions. We believe that this is a fair and reasonable ask to ensure that current and future generations of Canadians with rare diseases have access to the transformative medicines that will enable them to achieve better health and a brighter future.

[24] Rawson, Nigel SB; Lawrence, Donna (2020). New Patented Medicine Regulations in Canada: Updated Case Study of a Manufacturer's Decision-Making about a Regulatory Submission for a Rare Disorder Treatment. *Canadian Health Policy*, January 2020. Toronto: Canadian Health Policy Institute, www.canadianhealthpolicy.com