

February 14th, 2018

Karen Reynolds
Executive Director, Office of Pharmaceuticals Management Strategies
Strategic Policy Branch, Health Canada
Ottawa, Ontario
K1A 0K9

Dear Ms. Reynolds,

RE: Response to Consultation on Proposed Amendments to the Patented Medicines Regulations

Executive Summary

Gilead Sciences, Inc. (Gilead) is an innovative, research-based biopharmaceutical company with a mission to advance the care of patients suffering from life-threatening diseases worldwide. Over the past 30 years, Gilead has been a key contributor to transforming patient outcomes in HIV/AIDS, Hepatitis C and B and is currently leading cure-focused research in HIV, HBV, hematology and oncology.

Gilead has a significant research and development (R&D) footprint and currently invests more than 23% of Canadian revenues into R&D in Canada.

Gilead is concerned about the proposed amendments to the PMPRB regulations. High uncertainty, unpredictability and risk in the regulation changes as proposed will negatively impact access to innovative new therapies as well as investment in R&D in Canada.¹

As an organization that delivers significant investment into Canada and has had the opportunity to deliver transformative pharmaceutical innovation in the HIV, HCV and now the oncology space, Gilead requests the following:

- i. Removal of the proposed economic factors from the regulation of maximum allowable list price as these create high unpredictability and business uncertainty and will serve to reduce access to innovative therapies for Canadians
- ii. Reconsideration of the proposed schedule of reference countries to include jurisdictions with similar levels of wealth and access to innovative medicines

¹ PMPRB Annual Report 2016 [Online] Available: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1334>

- iii. Removal of the proposed regulation change requiring reporting of confidential net pricing arrangements as this will result in a paradoxical reduction in savings for Canadian payers and create significant ramifications around the use of privileged information.

Gilead recommends a considered approach to more fully understand and assess i) implications for patient access to innovative new medicines and ii) economic impact for the pharmaceutical and biotechnology industry and, consequently, for research and development investment in Canada. Gilead welcomes the opportunity to have a constructive dialogue with government to explore alternative solutions.

1.0 Gilead Corporate Introduction

1.1 Gilead – Canadian Infrastructure and Investment

Gilead Sciences, Inc. (Gilead) is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. Over the past 30 years, Gilead scientists have contributed to significant advances in areas of high public health impact such as the treatment and prevention of HIV/AIDS, the treatment of influenza, hepatitis C and B and other infectious diseases. We are leading in scientific developments of new therapeutics, including novel cell therapy technologies which have the potential to further transform cancer care.

In Canada, Gilead has invested significantly across our national, Ontario and Alberta based operations and employs more than 500 people across the country. With 18 marketed products, we work in the therapeutic areas of HIV/AIDS, liver diseases, oncology, and respiratory diseases with over 100 of our Canadian employees supporting full-scale commercial, medical, regulatory, finance and legal operations.

Gilead supports the development of new innovative therapies with its Canadian process and research facility located in Edmonton, Alberta. The site, with more than 400 additional highly skilled employees, manufactures active pharmaceutical ingredients (APIs) for the company's investigational compounds as well as for some commercial products, and provides technology transfer and support to Gilead's commercial API manufacturing sites and partners around the world. In 2014 Gilead acquired an additional 10 acres of land in Edmonton to support several ongoing phases of facility expansion.

Gilead also leverages Canadian contract manufacturing capabilities to serve both local and global production. Fully one third of worldwide Gilead tablet requirements are produced via Canadian contract manufacturing.

Canadian R&D Investment: As an innovative, research-based company, Gilead supports close to 100 active clinical studies in Canada across 274 Canadian sites in addition to 15 Investigator Sponsored Research (ISR) studies initiated by Canadian investigators.

Gilead's overall research and development (R&D) investment in Canada, exceeded 23% of our Canadian revenues in 2016 when calculated with updated methodology aligned with the recently published Ernst & Young report.² When calculated by PMPRB using methods established 30 years ago with strictly SR&ED criteria, Gilead R&D investment was determined to represent 16.4% of Gilead Canada revenues in 2016, with a compound annual growth rate of 16%.

1.2 Gilead – Innovation and Impact on Patient Care

Below are examples of major therapeutic advancements that Gilead has delivered and is currently developing, substantiating our concerns around the type of clinical innovation that could be impacted in Canada with the level of uncertainty and unpredictability that would result from the proposed regulatory changes.

HIV/AIDS: For over 30 years, Gilead has focused on the development of antiretroviral therapies to treat HIV/AIDS, transforming a once-fatal disease into a manageable condition. Successive improvements to the efficacy, safety and tolerability profile of HIV treatments, including the innovation from Gilead to develop the first single tablet regimen, have contributed towards the advancement of the World Health Organization (WHO) 90-90-90 goal of controlling and managing HIV (90% diagnosed, 90% treated, and 90% with undetectable viral load).³ Gilead is also committed to developing strategies that prevent the transmission of HIV and continues to support research in this area.

Research Focus - HIV Cure: Building on these advancements, and on the paradigm of prevention-treatment-cure, Gilead is conducting early-stage clinical research to identify novel agents and strategies that could play a role in eradicating HIV infection in the body. Gilead has invested significantly in this comprehensive research program with the goal of developing a cure for HIV and helping to bring an end to the HIV epidemic.

Hepatitis C – Cure Now Available for Patients: Gilead has helped revolutionize the treatment of chronic hepatitis C virus (HCV) infection, Gilead has developed innovative sofosbuvir-based direct acting anti-viral (DAA) therapies that now offer cure rates as high as 95-99 percent across

² Ernst & Young. (2017). *Innovative Medicines Canada: Data Analytics and Members' Economic Footprint and Impact in Canada 2017* [Online] http://innovativemedicines.ca/wp-content/uploads/2017/10/20171030_EY-REPORT_IMC_FINAL.pdf

³ UNAIDS. (2017). *90-90-90 - An ambitious treatment target to help end the AIDS epidemic* [Online] Available: <http://www.unaids.org/en/resources/documents/2017/90-90-90>

all genotypes (1-6) of HCV infection⁴ with a much shorter treatment period and much higher tolerability versus prior regimens.

These new DAA's avoid the serious short and long term impacts associated with HCV - including liver fibrosis, liver transplant, liver cancer and death - directly benefiting patients while attenuating pressure on the health system with these avoided outcomes. These transformations in care contribute towards the global fight against viral hepatitis and to public health efforts to achieve the WHO goal of eliminating HCV infection by 2030 – a goal supported by the federal government in Canada.

Oncology - CAR-T & TCR Technology: Gilead is leading the development of innovative chimeric antigen receptor (CAR) and T cell receptor (TCR) engineered cell therapies designed to empower the immune system's ability to recognize and kill tumours. Gilead led in this area with the recent approval of the first chimeric antigen receptor T-Cell (CAR-T) therapy for the treatment of aggressive lymphoma in the U.S. This is expected to be the first of a number of indications for Gilead cell therapies that have the potential to revolutionize and cure difficult to manage solid tumours and hematological malignancies, addressing an urgent need for cancer therapies that offer improved survival and tolerability.

1.3 Global Access to Essential Therapy

Over the past 15 years, Gilead has developed and implemented a robust program to ensure access to its HIV, HBV and HCV medicines for people in resource-limited countries where these infectious diseases may hit the hardest. Gilead was the first pharmaceutical company to sign an agreement with the Medicines Patent Pool, a United Nations-backed initiative to promote the licensing of drug patents for use in low-income countries.⁵

Gilead makes it a priority to increase access to its life-saving medicines at no-profit pricing in over 100 resource-limited countries, with substantial price reductions in middle income countries.⁶ Due to these efforts, the number of people in developing countries receiving Gilead antiretroviral therapy for HIV has increased from fewer than 30,000 in 2006 to over 10 million in 2017.⁷ In 2014, Gilead announced arrangements with generic pharmaceutical manufacturers in India to expand access to Gilead's HCV products in 91 developing countries. Over 650,000 people in these countries with high HCV burden have gained access to curative therapy with the Gilead HCV portfolio at low cost.

⁴ Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, *et al.* Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015;373(27):2599-2607.

⁵ Medicines Patent Pool. (July 12, 2011). *Medicines Patent Pool Announces First Licensing Agreement with a Pharmaceutical Company* [Online] Available: <https://medicinespatentpool.org/mpp-media-post/medicines-patent-pool-announces-first-licensing-agreement-with-a-pharmaceutical-company/>

⁶ Gilead Sciences. (October 2014). *Product Pricing and Patient Access* [Position statement].

⁷ Gilead Sciences. (November 2016). *Scaling up Antiretroviral Treatment Sustainably: Gilead Sciences Programs in Developing Countries* [Online] Available: <https://www.gilead.com/-/media/files/pdfs/other/hiv%20access%20background%20us%20112816.pdf>

In order to achieve ongoing innovation and widespread drug access, we believe developed nations such as Canada should enable pricing policies that reflect the value of innovation for Canadian patients. Clear and predictable pricing in developed nations such as Canada will allow us to develop and support, along with governments, programs that enable access to drugs in the developing world.

1.4 Gilead Position on Proposed Regulatory Changes

Gilead is supportive of solutions that optimize access to innovative therapies in an affordable and sustainable way. Gilead is also supportive of solutions that create a predictable business environment and enable clear and accelerated decision-making around new product launches and investment in Canada.

The proposed changes to the *Patented Medicine Regulations* pose barriers to these principles from multiple standpoints. The proposed regulation changes:

- i. Foster significant business uncertainty that could easily result in reduced and delayed access to new innovative medicines in Canada
- ii. Create a barrier to international trade through unpredictable devaluation of intellectual property rights
- iii. Present an obstacle to pharmaceutical investment in research, development and manufacturing in Canada, an issue that has not been adequately reviewed or assessed in the Health Canada cost-benefit analysis or the Regulatory Impact Analysis Statement.

As a global organization with i) 23% of our Canadian revenues invested in R&D in Canada, and ii) significant investment in research and development programs focused on delivering future cures for HIV, HBV and different forms of cancer, Gilead is very concerned about the issues noted above.

The regulations as currently drafted should be reconsidered and a new, more balanced approach applied. Canadian pharmaceutical prices are referenced, both formally and informally, by other markets. Global organizations can be expected to wait until they are able to make reasonably informed decisions about the Canadian market, thus increasing the likelihood that some innovative products will have a delayed market opportunity in Canada or no market opportunity at all.

Innovative models, defined directly with payers, are much more likely to meet payer-specific needs and deliver both affordability and valued health care innovation to Canadians. The negative trade-offs associated with the proposed regulation changes must be seriously considered and understood to ensure that federal and provincial policy decisions support a balanced set of desired outcomes for health care, innovation and economic development in Canada.

2.0 Inputs on Proposed Regulatory Amendments

2.1 Introduction of New, Economics-Based Price Regulatory Factors

Summary:

- The proposed application of economics-based price regulatory factors is highly problematic as these metrics are by their nature assumptions-driven; Based on the wide range of potential variability in the application of these factors by PMPRB, there is no feasibility for a manufacturer to predict in advance what the maximum allowable price threshold of a new product would be.
- In circumstances with this level of local and global financial risk due to the potential for significant, unknown changes in the globally transparent list price of a drug following its launch in Canada, decisions by global organizations regarding whether and when to launch innovative medicines into Canada will be negatively impacted.
- The application of Cost/QALY, market size and GDP should be removed from the draft regulations due to the lack of clear and predictable outcomes. From a commercial perspective, no viable business can make reasonable decisions with this level of uncertainty.
- Proposals to make economic factors mandatory for PMPRB consideration, such that they apply to the entire Canadian market, is an excessive, disproportionate and unreasonable extension of federal regulatory powers.

In the proposed draft regulations, Health Canada has introduced the application of three economic factors that would be used in determining the maximum allowable price for patented medicines: cost/QALY, market size, and GDP. Feedback on the application of the proposed economic instruments is provided below.

2.1.1. PMPRB is the wrong policy tool to determine affordability and willingness-to-pay

Economic factors are considerations for payers, not regulators, in the health system decision-making process around new medicines.

The PMPRB, as a quasi-judicial federal board, is poorly positioned to make determinations of willingness and ability-to-pay for all potential purchasers of patented medicines. These evaluations should be made by those who are paying for new therapies, including individuals, employers and public payers.

The application of cost-effectiveness evaluations is, in practice, exceptionally complex. Methods by necessity involve assumptions, inferences, and jurisdiction specific demographic, societal, and economic considerations that, in turn, influence outcomes. Assessments of value and willingness-to-pay may be different across private, public and cash payers, across differing environmental circumstances and across different therapeutic areas. Given that pharmacoeconomic outcomes are developed through assumption based modelling, these are

not appropriate metrics to be applied in “black and white” fashion by a national regulator in the establishment of maximum allowable price.

Moreover, even with the availability of a cost-effectiveness evaluation that is mindful of jurisdictional factors, a persistent challenge would be the application of an Incremental Cost-Effectiveness Ratio (ICER) and the appropriate threshold for cost-effectiveness. It is well accepted that the use of Incremental Cost Effectiveness Ratios (ICERs) and Quality Adjusted Life Years (QALYs) is appropriately balanced as one consideration in a health technology assessment that informs payer assessment of value and willingness to pay in addition to burden of illness, unmet need, clinical effectiveness, budget impact, patient input and in the case of Quebec, societal considerations. While QALYs serve as a useful starting point for value assessment, they fail to capture the full health, well-being, and social benefits of interventions that are important to patients and other stakeholders.

Market Size Considerations: Budget impact analyses are required and assessed as part of provincial and private market reimbursement submissions. They take multiple factors into consideration including public versus private population covered and the provincial therapeutic and policy environment. Factoring market size into the process to regulate a maximum allowable list price, in addition to being highly unpredictable in terms of expected outcomes, would have important implications on assessment for new innovations.

A case in point is the opportunity for a new, curative treatment which represents an immediate gain for patients and the health care system. A curative treatment, however, would be negatively impacted by the initial, upfront demand for a product post launch as patients and physicians sought to access the cure. This would lead to the undervaluation of breakthrough innovation due to the potential upfront cost with no consideration for the long term price amortization that is customary for chronic treatment. Ramifications of this application of market size could be to limit access and to halt further therapeutic advancements for cost-effective curative treatments.

Similarly, for a first agent entering a new, less defined therapeutic area, there is significant increased risk and uncertainty placed on the patent holder if market size is used as a defining factor of price at the regulatory level rather than based on discussions with payers where emerging understanding of the newly defined space can be factored in over time. Epidemiology data and market estimates may be limited at the outset for a first entry medication and “black and white” application of market size assessments are likely to be additionally punitive for the patent holder.

2.1.2 Application of economic factors will significantly increase business uncertainty resulting in reduced access to innovative therapies for Canadians

Stakeholder feedback in consultations to date have noted that the regulations should require the PMPRB to “apply ‘bright line’ rules that are consistent with international best practices and

provide predictability to stakeholders.”⁸ The proposed regulation changes, however, greatly diminish predictability and create significant uncertainty for manufacturers that can impact the decision to launch in Canada.

Under the current PMPRB guidelines, there is relatively high predictability for manufacturers, in terms of what prices will be considered acceptable, and when prices will be evaluated as “excessive.” Application of the appropriate pricing tests across PMPRB countries and across therapeutic comparators yields a clear predictive range of what the PMPRB maximum average potential price (MAPP) will be prior to a new product launch. This allowable price range can be calculated and presented to internal local and global pricing decision makers involved in the approval of the list price for the drug prior to launch with a high level of confidence, enabling clear and expedited global decision-making relative to launch into Canada.

Embedding economic factors in the regulations would significantly increase business uncertainty and directly impact important commercialization and investment decisions to the detriment of Canadians. The application of economic factors, by their nature, have a measure of subjectivity that will be impossible for manufacturers to predict in advance. The weight and cumulative impact of these factors as they are layered together to establish price maximums will be highly complex and also impossible to predict.

In this context, a Canadian organization would be seeking global approvals to launch an innovative product armed only with an educated guess on what the final allowable price might be and with the risk that the global, transparent list price of the drug could change markedly later in the post launch period when the PMPRB assessment is complete. This level of unpredictability and uncertainty is inconsistent with the principles of predictability, fairness and good governance.

The level of uncertainty is compounded by the global context for drug development and commercialization. Canadian pharmaceutical prices are referenced, both formally and informally, by other markets. Given the level of local and global risk, global organizations can be expected to wait until they are able to make reasonably informed decisions about the Canadian market, thus increasing the likelihood that some innovative products will have a delayed market opportunity in Canada or no market opportunity at all. This level of regulatory uncertainty would be considered unreasonable for any industry.

Unlike regulatory submissions to the European Medicines Agency (EMA), which address approvals for multiple European countries in one submission process, the decision to input a regulatory dossier to Health Canada is a stand-alone decision with significant stand-alone investment. The higher the unpredictability and uncertainty in the Canadian environment, the lower the likelihood the Health Canada submission will be prioritized.

⁸ Health Canada. (May 2016). *Protecting Canadians from Excessive Drug Prices: Consulting on Proposed Amendments to the Patented Medicines Regulations*.

While Health Canada and HTA agencies are collaborating in order to accelerate access to innovative treatments to Canadians, these proposed regulatory amendments serve to contradict this intent. Economic factors are already extensively applied at other levels of evaluation, negotiation and reimbursement decisions, especially those related to affordability and should not be under the purview of PMPRB.

Given the level of business uncertainty they cause, and the resulting impact on access to innovative medicines for Canadian patients, the proposed application of economic factors by PMPRB should be removed from the draft regulations.

2.2 Proposed Update to the Schedule of PMPRB Price Reference Countries; Inconsistent with Canadian Economic Status and Standing Regarding Access to Medicines

Summary:

- Health Canada has offered no compelling rationale for changing the basket of countries to bring the maximum average prices in Canada down to the median of the OECD, when Canada's economic status is well above the OECD median.
- Similarly, five of the seven new countries proposed in the PMPRB12 sit below the OECD median in terms of the percent of new medicines launched (South Korea – 33%; Netherlands – 36%; Japan – 38%; Australia – 40%; Belgium – 45%) while Canada sits above the median at 61%.⁹
- Setting benchmarks with countries that are not comparators in economic standing and that have significantly lower access to new therapies does not appropriately serve the health care goals and expectations of Canadians.
- The proposed schedule of countries should be reconsidered to include jurisdictions with similar levels of wealth and access to innovative medicines (i.e. G10).

Canadians place a high value on health care and on access to innovative medicines to meet their health needs. Currently, as measured by PMPRB, Canada is among the top 5 OECD countries as determined by new medicine launches.¹⁰

While Health Canada and PMPRB have been clear in the rationale to exclude the United States from the schedule of countries, there is very little clarity around the choice of countries included in the proposed revised schedule of 12 international reference countries. While the driving rationale appears to be the goal to benchmark on the OECD median, this does not align with the fact that Canada's economic status sits well above the OECD median. In addition, five of the seven new countries proposed in the PMPRB 12 sit below the OECD median in terms of the percent of new medicines launched (South Korea – 33%; Netherlands – 36%; Japan – 38%;

⁹ Patented Medicine Prices Review Board. (April 2017). *Meds Entry Watch*, 2015.

¹⁰ Patented Medicine Prices Review Board. (2016). *Annual Report 2016* [Online] Available: <http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1334#a9>

Australia – 40%; Belgium – 45%) while Canada sits above the median at 61%.¹¹ Benchmarking on countries with reduced access to new medicines seems to conflict with Canadian health care values and expectations. External price benchmarks should at minimum be based on comparisons with like countries.

Practically, the expectation of delayed launch timing into proposed additional lower access reference countries will create additional business uncertainty as manufacturers will need to manage multiple “waves” of unknown impact on the maximum allowable price as additional reference countries come on line. Ongoing uncertainty about the allowable transparent list price will create disincentives to launch innovative medicines in Canada.

Gilead recommends reconsideration of the schedule of countries to better fit with Canadian expectations around access. The currently defined G10 list of countries would be more appropriate as economic and access comparators.

2.3 Reporting of Confidential Price Arrangements Creates Significant Legal Challenge

Summary:

- Regulation change requiring reporting of confidential net pricing arrangements will result in a paradoxical reduction in savings for Canadian payers and create significant ramifications around the use of privileged information.

Prior to the introduction of the new proposed PMPRB regulations, there was certainty for signatories to either a private or public product listing agreement that net prices would remain confidential. Confidentiality of financial terms recognizes that the pharmaceutical market is global and allows manufacturers more flexibility to address plan specific challenges to affordability and value-for-money.

Acknowledging that the draft regulation changes indicate that the reporting of confidential price arrangements would be considered privileged, the Regulatory Impact Analysis Statement (RIAS), which accompanied the draft changes, includes the following statement:

The PMPRB currently regulates the non-excessive price of a medicine based on the prices of other medicines in the same therapeutic class for sale in Canada. Since that price information does not include third-party price adjustments, the prices of comparator products that subsequently enter the market are often inflated (as the price ceilings for those medicines are determined in relation to an inflated list price of the existing medicine, rather than the actual price paid in Canada). As a result, the therapeutic class comparison tests yield price maximums that are higher than they would be if the actual price paid were available to the PMPRB. Compelling actual price information, inclusive of all price

¹¹ *Ibid.*

adjustments provided by the patentee, would allow the PMPRB to include rebates in the calculation of the average transaction price.

It is difficult to reconcile how information about confidential expenditure limit arrangements reported to the PMPRB would be maintained as privileged if it is being applied to establish maximum allowable list prices for new category entrants. The communication of the maximum allowable price to the manufacturer of a new entrant provides a clear indicator of the scale of confidential agreements in place in a given category as, presumably, a federal regulator would need to provide a transparent explanation of the price maximum that they would be enforcing. Similarly, the introduction of a transparent list price for a new category entrant that differs significantly from the list prices of available comparators provides a clear, publicly visible indicator of the scale of pre-existing confidential agreements.

This proposed model paradoxically is very likely to reduce the value of expenditure limit agreements that manufacturers are able to define with public and private payers in Canada and creates significant legal considerations around disclosure of privileged information. In these circumstances, manufacturers will not be in a position to continue to provide significant rebates to payers, leading to higher costs and/or lower access to therapies reimbursed by public and private plans.

The collaborative and collective effort of negotiating value arrangements should continue to reside between manufacturers and payers. The existing process and effort continues to work in ensuring patient access to innovative medicines in Canada, while allowing flexibility to align customized solutions to meet the affordability needs of individual plans and jurisdictions.

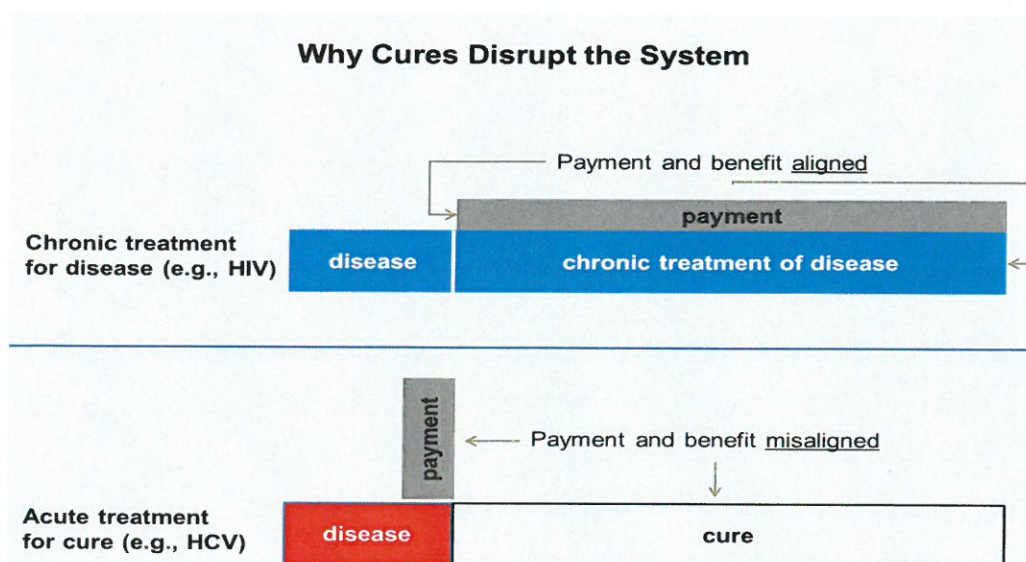
3.0 HCV “Case Study”

3.1 Curative Therapy: Implications of Proposed Regulation Changes

When breakthrough drugs become available, price cannot be the only lever to ensure sustainable access. Health system sustainability is only possible with the early and continual involvement of all stakeholders, including drug companies, patients, payers, governments and providers.

Curative therapies like direct acting antivirals (DAAs) for HCV have disrupted health systems (see Figure 1). Unlike chronic therapies, which align payment to benefit over a long-term horizon, delivery of a curative therapy requires up-front costs and short-term budget impact for a long term or lifetime benefit. Learning from the DAA analogue, curative therapies can also result in a short term accelerated bolus of demand as patients who are diagnosed and linked to care actively seek the cure in the immediate post launch period, further exacerbating the short term budget impact associated with the long term curative benefit.

Figure 1:



Based on the scoping document released by PMPRB, a curative therapy would be deemed to be a high risk agent and would be subject to the most stringent sequence of price tests to determine the maximum allowable price.

Seeking to manage affordability of a cure with a lens strictly on the up-front cost of therapy is a model that doesn't acknowledge or address the disruptive factors at play. Counter-intuitively, this approach serves to dis-incentivize investment in the development of a cure in favour of investments in development of chronic, long term therapies.

Innovative models that help amortize the cost of benefit over a longer time span are more appropriate for application in a cure model both from the lens of affordability as well as health system value. An innovative payment model of this nature is best defined directly with the payer to ensure that system needs and considerations are appropriately met and that value and affordability are better balanced.

3.2 Importance of Incremental Innovation

The DAA category also provides a notable case example of the importance of avoiding disincentives to incremental innovation. In 2013, the launch of sofosbuvir was greeted as a transformative entry into the HCV treatment landscape, offering significantly higher cure rates than prior standard of care therapies with a significantly improved safety profile.¹²

¹² Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, *et al.* Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015;373(27):2599-2607.

The launch of sofosbuvir was followed in 2014 with the launch of sofosbuvir/ledipasvir and, in 2016, with the launch of sofosbuvir/velpatasvir. Both new entry regimens further increased cure rates into the 95-99% range¹³ and created simple, single tablet regimen options for the majority of patients without the need to incur additional cost or tolerability considerations with the addition of ribavirin. These two new entries further expanded the population of patients eligible for curative therapy to include patients with all genotypes (1-6) of HCV, and, in the case of sofosbuvir/velpatasvir, delivered cure rates in the >95% range even for the genotype 3 HCV patients who have traditionally had the lowest cure rates and the most challenging prognosis.¹⁴

Early access and clinical success of the original sofosbuvir platform enabled the company to pursue its ongoing research and investments to further advance the cure rate and simplicity of successive new entries. Despite the level of transformative impact the launch of sofosbuvir originally had on the treatment of HCV in Canada in late 2013, as of 2017, sofosbuvir has been essentially rendered obsolete as a treatment regimen due to the significant further advancements seen with sofosbuvir/ledipasvir and sofosbuvir/velpatasvir.

It is not clear that subsequent waves of new, more effective therapies within a class would have become available in a timely fashion in Canada if the new regulations had been in place.

3.3 Impact and Implications

Prior to DAA availability, estimates from the Public Health Agency of Canada have indicated that cases of HCV-related end-stage liver disease, hepatocellular carcinoma (HCC), liver transplantation and death would increase by approximately 20% to 80% between 1997 and 2027.^{15,16} Administrative data from Calgary, Alberta, has demonstrated in a real world setting that liver-related hospitalizations, hospital costs and mortality due to HCV rose even faster than this estimate, with a four-fold increase between 1994 and 2004.¹⁷

With the proposed regulatory amendments to the PMPRB process and resulting business uncertainty, would the standard of care of Hepatitis C in Canada have advanced to the stage that it has today with such rapid evolution? How many liver transplants and how many cases of liver cancer may have been experienced by patients and the health care system while Canadians waited for the entry of these successive innovations? How many long term health effects of advancing liver fibrosis may have been incurred due to worsening disease?

¹³ *Ibid.*

¹⁴ Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, *et al.* Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med.* 2015;373(27):2608-17.

¹⁵ Remis RS / Public Health Agency of Canada. (2009). *Modelling the Incidence and Prevalence of Hepatitis C Infection and its Sequelae in Canada, 2007.*

¹⁶ Myers RP, Krajden M, Bilodeau M, *et al.* (May 2014). *Burden of disease and cost of chronic hepatitis C virus infection in Canada.* *Can J Gastroenterol.* 2014;28(5):243-50. doi: 10.1155/2014/317623.

¹⁷ Myers RP, Liu M, Shaheen AA. (April 2008). The burden of hepatitis C virus infection is growing: a Canadian population-based study of hospitalizations from 1994 to 2004. *Can J Gastroenterol.* 2008;22:381-7

4.0 Conclusions and Recommendations

High uncertainty and risk in the regulation changes as proposed would devalue global and Canadian intellectual property, erode the value of innovation and consequently impact access to innovative new therapies as well as investment in R&D in Canada. As an organization that delivers significant investment into Canada and has had the opportunity to deliver transformative pharmaceutical innovation in the HIV, HCV and now the oncology space, Gilead requests the following:

- i. Removal of the proposed economic factors from the regulation of maximum allowable list price as these create high unpredictability and business uncertainty and will serve to reduce access to innovative therapies for Canadians
- ii. Reconsideration of the proposed schedule of reference countries to include jurisdictions with similar levels of wealth and access to innovative medicines
- iii. Removal of the proposed regulation change requiring reporting of confidential net pricing arrangements as this will result in a paradoxical reduction in savings for Canadian payers and create significant ramifications around the use of privileged information.

Gilead recommends a considered approach to more fully understand and assess i) implications for patient access to innovative new medicines and ii) economic impact for the pharmaceutical and biotechnology industry in Canada and, consequently, for research and development investment in Canada. Gilead welcomes the opportunity to have a constructive dialogue with government to explore alternative solutions.

Sincerely,



Kennet Brysting
General Manager
Gilead Sciences Canada, Inc.