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DEVELOPING A NATIONAL STRATEGY FOR RARE DISEASES IN CANADA;

SOME NECESSARY CONSIDERATIONS

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Why do we need a policy for rare diseases?

First and foremost, a national strategy for rare diseases must go beyond the issue of access to drugs. The majority of rare diseases have no available treatment, so focusing only on access to existing drugs is also to ignore the majority of patients with rare diseases. The whole discussion document "Building a National Strategy for High-Cost Drugs for Rare Diseases", and the whole presented strategy for rare diseases, only emphasizes high-cost drugs an it is far from an optimal step to tackle the issue of rare disease in Canada.

Patients with rare diseases (and their families) have important needs beyond pharmaceuticals that must also be taken into account. Many patients or caregivers are completely left to themselves with little resources when it comes to rare diseases. When there is a rare disease in a family, you will often need years of clinical visits before finding a physician that will finally diagnose the issue correctly. Normally the family is already overwhelmed just trying to navigate the health care system, but the issue goes beyond health care. Buying an appropriate wheelchair, adapting the house or the car, lost income because of constant hospital visits or because one parent needs to stay at home at all time with a sick kid - these are also key issues for families dealing with rare diseases. It is a bit odd that governments can pay $300,000/year for a drug that will slow the progress of a rare disease by 15%, but a family that needs to provide 24 hours a day 7 days a week of care for a sick kid cannot receive a hundredth of that amount to pay for a professional caregiver that could help the family for specialized care and provide some respite. In the current system, most provinces consider that psychological help is not an essential service to be provided to these families. Also, specialized services to help families navigate the journey of rare diseases would be most welcome, for example just by explaining what resources are available in terms of health care or social assistance. A national strategy should focus on how to best help patients with rare diseases, not on how we can spend more on drugs.

Issue 1: How to improve patient access to high-cost drugs.

For many patients, one important issue remains access to high-cost drugs. Before tackling the issue, let's begin with an example (I used a fictitious name but it is a real case).

The Case of Monica

Monica lives in British Columbia and turned 14 in January 2020, which is very bad news. Monica has a rare neuromuscular disease called spinal muscular atrophy (SMA, type 2), a progressive condition that is slowly robbing her of her strength and her ability to move and breathe. She was full of hope, however, because new cures were recently discovered. A new drug called *Spinraza* treats SMA, and was approved by Health Canada in 2017. The drug costs

$750,000 for the first year of treatment (and then $375,000 for each subsequent year for the rest of one's life). It slows the disease and allows some recovery for some patients. Her parents' drug plan will not reimburse the drug, but the province offers catastrophic coverage when a household pays more than 4% of their net annual income on prescription drugs, for drugs listed on the province's formulary. In order to be listed on the formulary, a new drug must demonstrate cost-effectiveness. In the case of *Spinraza*, the product was not cost-effective but the province negotiated a confidential rebate with the drug company *Biogen*. In the end, the province announced their decision about reimbursement:

> -The province will reimburse the drug for all patients with type 1 SMA (the most aggressive form of the disease).
> -The province will reimburse the drug for patients with type 2 SMA (where the disease develops more slowly) only if they are under 13.
> -The province will not reimburse the drug for any patient with type 3 SMA (the mildest form of the disease).

"It's beyond me and it's baffling," said Monica who waited two years for the province to make a decision about reimbursement. "It makes you want to punch a hole into the wall and scream, and I wouldn't be surprised if it makes people really depressed and sad inside."

Monica has hope, however, because another drug company *Novartis* just announced a revolutionary gene-therapy for SMA called *Zolgensma*. The drug is promising for patients with type 2 SMA, as it modifies the patient's genes in a way that could cure the disease. The price tag, however, is $2.3 million for one treatment, which makes *Zolgensma* the most expensive drug ever sold. Most drug plans refuse to reimburse the drug but SMA patient groups around the world are mobilizing to force governments to reimburse the cost of the drug. In order to show how efficacious the drug is (and put pressure on drug plans), *Novartis* created a global lottery and will gave away 100 treatments. However, Monica could not qualify for the lottery because of her age. Her only glimmer of hope for a treatment is that another company, *Roche*, has a new drug (*Risdiplam*) in its pipeline for type 2 SMA patients. The drug looks promising, but, again, it is unlikely that the drug would be affordable for the province.

The case of Monica offers just a taste of the complexity of the issue of rare diseases, and of the lived experience of patients who constantly face hostility from bureaucratic systems that treats them like unwanted burden. We need a system that can make sense for patients, with clear rules, fair and transparent decisions and that can accompany patients (and their families) in their journey.

The discussion document proposed 4 options to improve patients' access to high-cost drugs: 1-A single framework for decision making on high-cost drugs; 2-A transparent co-ordinating body; 3-Patient and clinical engagement; and 4-Co-ordinated support for research on rare diseases in Canada. It seems self-evident that we need all of the 4 options mentioned:

Explanation why we need to embrace all 4 options

There is a running joke among drug companies' employees that if you have a new staffer in the market access division, send them to Canada: if they survive the Canadian complexity,

they can go work anywhere else in the world. The current fragmented Canadian system is pure non-sense. Having a central agency managing a national drug formulary for all Canadians was one of the central recommendations of the Advisory Council for the Implementation of National Pharmacare. Such centralization and coordination should be a top priority. Other OECD countries have a national formulary of drugs that will be reimbursed for the whole population and that gives them a lot of bargaining capacity to force drug companies in lowering their prices if they consider that the therapeutic value they get is not worth the cost. In a system with a centralized drug plan for the whole population, health technology assessment can provide good guiding principles to avoid wasting money and make recommendations based on the best available evidence.

Canada is completely fragmented when it comes to drug coverage: 30% of the population (mostly seniors and low-income families) is covered through public plans and 60% of the population (mostly workers and their dependents) is covered through private plans. Coverage is fragmented between private and public plans, and between provinces. We have around 100 public drug plans in Canada and around 100,000 private drug plans, which all cover different drugs with their own set of deductibles and co-pays. And many Canadians still do not have any coverage at all. Private drug plans often do not use health technology assessment and have an "open formulary" – they will accept to reimburse anything approved by Health Canada, whatever the price is.

When a drug is approved by Health Canada, it simply needs to show that it works better than a placebo. In order to be reimbursed by public drug plans, it must show that it provides value-for-money. The assessment for value is done through the Canadian Agency for Drugs and Technologies in Health (CADTH) and its Common Drug Review. Quebec is different and uses another agency called INESSS. CADTH does the health technology assessment and then simply provides recommendations to provinces in terms of how much they should accept to pay for a drug. Note that the official price of the drug is not the real price and drug companies normally offer confidential rebates of 20-25% on average for their patented drugs. Each province negotiates with drug companies to see if they can reach a "product-listing agreement" to list the drug on their provincial formulary. For some drugs the rebate can be up to 90%. Note that provinces started collaborating in their negotiations and they now normally negotiate together through the Pan-Canadian Pharmaceutical Alliance (PCPA), a product of the Council of the Federation. However, even if a deal is struck by PCPA, the provincial budget will determine if each province can accept the deal. It is not unusual to see Alberta and Ontario listing a drug while Nova Scotia or New Brunswick will not list the drug because of their tighter budget. It has become a difficult situation for drug companies. They have all these negotiations just to have public plans reimburse the drug for 30% of the Canadian population. In other OECD countries (excluding the US) you have one central agency managing the drug plan for the whole country and the whole population. There is one negotiation on prices and one decision that applies to the whole country. This way, the system makes much more sense to patients, drug companies and health care professionals.

Beyond a centralized agency managing transparently a single framework (or national formulary), we also need to make sure that we engage with patients in every step of the process of drug approval and drug coverage. Such a system can work only in partnership with

patients, not as a bureaucratic obstacle that is imposed on patients as it is too often the case right now.

Finally, public authorities, and especially Health Canada, could play an important role to co-ordinate support for research on rare diseases in Canada, for example by building the necessary infrastructure to allow clinical trials for drugs for rare diseases. Currently, the way we do clinical trials in centralized research centers is not adapted for diseases with so few patients. Health Canada and the Canadian Institutes for Health Research could work together to finance the decentralization of some clinical trials in Canada.

Issue 2: How to ensure coverage decision are based on best available evidence?

Based on the discussion document, it is again self-evident that we need all 4 proposed options: 1-Innovative approval and coverage models; 2-A national expert panel; 3-A national data system; 4-Independent networks. All this can be achieved by a central agency, as proposed in the first section, but only if it works at arms-length of governments. Coverage decisions must be made based on expertise and evidence, not by panicked health ministers due to newspapers headlines.

A centralized agency can also be very interesting for orphan drugs that often arrive on the market with little data about their efficacy since we cannot have data from large clinical trials and the testing before the drug hits the market is much more limited. A central agency can negotiate not only on drug prices but also on clinical efficacy. For example, if a very expensive drug hits the market with little data about its efficacy, a central agency managing the drug plan for the whole population can negotiate that the drug will be reimbursed only if it provides actual therapeutic benefits to the population, or even on a patient-by-patient basis. We call this "outcomes-based risk-sharing agreements", or "coverage with evidence-development". In fact, we can call this whatever we want and negotiate whatever we want.

The necessity for the collection of evidence and the collaboration with other health technology assessment organizations (domestic or abroad) is a no-brainer. This can be done most effectively through a centralized agency working at arms-length of partisan politics.

Issue 3: How to ensure sustainability when spending on orphan drugs

We often take for granted that in a system where pharmaceutical innovation is organized around the patent system in which innovators can recoup their R&D costs based on the market exclusivity they obtain for their product, we must make an exception for rare diseases

otherwise no research would be done for them. This is true in theory but the reality is more complex. More profits for drugs for rare diseases will not necessarily create more investment in R&D. In fact, the massive profits in the pharmaceutical sector have been used instead for industrial concentration through mergers and acquisitions, barring the way to new innovative companies. Share buy-backs are also at an all-time high. You now have drug companies specializing on ultra-rare diseases, producing like three products for a handful of patients across the globe and still ranking among the largest global 500 companies in terms of market value. The commercial success is based on demanding astronomical prices for drugs that were mostly developed in the public sector or by other companies. One could call this capitalizing on despair.

Strensiq can be a good example to illustrate the point. *Strensiq* is a drug for an ultra-rare bone disease called hypophosphatasia. The basic research was done by academics at Montreal universities with public funding. Once the research team found the mechanisms to tackle the disease and discovered potential silver bullets, the product development was done by the start-up *Enobia Pharma*, directed by a great academic researcher associated with the University of Montreal. The company also benefitted from important tax credits. Note that this is now the standard way of doing things. Basic research is mostly done through public funds and when you have a silver bullet, you launch a start-up to develop the drug. However, if you can end up with a good drug for patients, most start-ups cannot even try to compete with larger companies to market drugs, so they prefer to simply be acquired by larger companies. *Alexion* acquired *Enobia* in 2012 and it now demands such a price for *Strensiq* that public drug plans refuse to reimburse the product for most Canadians. Because the use of the drug depends on the weight of the patients, only newborn babies and toddlers have access to the drug at around $300,000/year. The drug can cost up to $2 million/year for adults and no-one is paying for that. A drug discovered by Canadian public researchers is becoming unaffordable for most Canadians who need it while transforming a foreign drug company into a profit-machine. In fact, following the acquisition of *Enobia*, Alexion's CEO, Leonard Bell, in 2014 became the world's highest paid pharmaceutical executive ever with total compensation of $227 million, an amount bigger than total payroll for all non-executive employees at the company. One can become somewhat skeptical about implementing a system that simply gives away more money to pharmaceutical companies without making sure that the money will be spent for research. Many might see the situation and consider that Canadians are paying twice for the drug; they pay for the R&D through grants, subsidies and tax credits, and then, because of the patent system that provide market exclusivity for the product, they pay unaffordable prices that make the drug inaccessible for most patients.

However, *Strensiq* is just an example and it is important not to fall into the Big Bad Pharma narrative. High prices do not necessarily mean that the company is price-gouging. Sometimes, just recouping R&D costs, or even just manufacturing costs like in the case of gene therapies, you still end up with treatments that might cost hundreds of thousands of dollars. If we say that we refuse to pay for these drugs because they are too expensive, then we might terminate important new pharmaceutical research. Maybe some technology is currently prohibitively expensive, but when the technology becomes more mature the cost can go down. By refusing to pay for such technology now, we might end up discarding what could become a new generation of life-saving and affordable technology. Reducing drug prices for

the sake of reducing drug prices can have important unintended consequences. In such cases, public research and manufacturing can be an interesting solution.

Take the example of *Glybera*, the first gene-therapy, developed for an ultra-rare blood disease. *Glybera*, was developed by Canadian academics at UBC in partnership with a European drug company. It was an extraordinary scientific advancement in which we were using a virus to go change the malfunctioning genes of patients, most of which on the planet, by the way, were in Saguenay Lac Saint-Jean. Contrary to *Strensiq*, the company spent so much on R&D that it went bankrupt. The drug was acquired some years ago by another European company, which was asking a million dollars for one treatment, the highest price ever seen at the time. No drug plan was willing to reimburse the drug and, instead of selling the drug at a lower price, the company decided to shelve the drug. Many people were furious about the decision and the National Research Council announced in 2019 that they would start producing the drug themselves through their public labs and would sell the drug at cost. It is a first in Canada where a public research lab will be producing a drug for rare diseases that drug companies are refusing to produce at an affordable price.

Note that more and more, many researchers claim that the patent system is reducing access to scientific knowledge and is slowing down innovation. For example, the Montreal Neurological Institute embraced "open-science" some years ago, making all its researchers share all their data and discovery. The idea was that the patent system and proprietary science had achieved its limit and they wanted to try a different model through systematic collaboration and sharing of data. Open science was used at first for covid-19 to sequence the genome of the virus and its evolution through variants. If it works in case of a global emergency, why wouldn't it work for rare diseases like SMA or Cystic Fibrosis?

Another example is the Structural Genomics Consortium in Canada. It is an interesting model, especially for basic research, and could serve as an interesting alternative to the patent system for some type of research. Public or not-for-profit labs working in open science can produce enough volume for ultra-rare disease, like in the case of Glybera. However, such public and not-for-profit labs might not always be the best tools to market drugs at a global scale. Nevertheless, they can establish public-private partnership with drug companies based upon the agreement that commercial drug products that arise from this collaboration will be priced affordably. This can be done through licensing agreements, in which a pharmaceutical company is granted rights to manufacture and sell a final product under the condition to sell it at an affordable price because it did not bear the full cost associated with developing the drug. Alternatively, the public-private partnership can enter into a non-exclusive licensing agreement with a drug company, which allows for more than one manufacturer to produce the product, creating competition and driving the price for the drug down.

Issue 4: Another idea: the regulation of patented drug prices through the Patent Act

When it comes to drug prices, Canada pays on average 25% more for the same patented drugs as compared to the median of OECD countries. Patented drug prices are not really determined

through regulations. Canada has, instead, a system to avoid excessive prices for patented drugs. We have the Patented Medicines Price Review Board (PMPRB) which regulates the official price of drugs (as compared to the real price of drugs once the confidential rebate is taken into account). The PMPRB is a creature of the Patent Act and must ensure that drug companies are not setting excessive prices. The maximum acceptable price is more or less based on the median price of a basket of seven comparator countries. This regulation, implemented in 1987, is now obsolete due to confidential rebates since PMPRB does not have access to these opaque confidential rebates. In a nutshell, Canada's watchdog for excessive drug prices does not know the real price of drugs. We regulate only official prices, and these are still more expensive than in comparable countries. And because of fragmented coverage in Canada, it also means that we do a terrible job negotiating confidential rebates relative to comparable countries.

Since 2016, PMPRB entered into a reform process to modernize its regulations. The reforms on the table are to provide PMPRB access to real drug prices; change the basket of comparator countries to better reflect the Canadian reality; include new criteria for excessive pricing like budget impact and value for money. However, the implementation of these regulations, postponed twice and now scheduled for July 2021, is still a bumpy ride.

Drug companies and patient groups are very reluctant to these reforms and are putting a lot of political pressure in the hope to get these reforms withdrawn or postponed. Their argument is simple: if drug companies make less profit, patients will have access to fewer new drugs. The argument, as we explained, is flawed. Drug companies are making record profits with new drugs that sometimes have very little additional therapeutic value as compared to what already exists. Currently 83% of new (and expensive) patented drugs marketed in Canada do not provide additional therapeutic value as compared to what already exists. PMPRB reforms would focus on value for money and budget impact, which would shift the incentives towards the production of therapeutic breakthroughs at affordable prices.

In the case of orphan drugs, some believe that the new regulations would reduce incentives for doing research on drugs that are not cost-effective, including drugs for rare diseases. In fact, the new regulations would allow drug companies to sell drugs at high price until a market threshold, and then all additional drugs sold would have to be rebated by a growing marginal discount rate. This way, we would ensure that drug companies would recoup their R&D costs and make a profit, while avoiding predatory prices. It would be the first time that a country would cap drug prices this way. If the system was paired with solid public investment for R&D and manufacturing for orphan drugs, the new regulations could allow preserving private financial incentives to develop orphan drugs while making drugs more affordable for all Canadians.

Conclusion

We all understand of complex the issue of rare disease can be, especially when it comes to accessing high-cost drugs. This submission emphasized six elements:

1-A strategy for rare diseases must go beyond the sole issue of paying for expensive drugs.

2-We need a centralized agency at arms-length of governments managing transparently and based on best available evidence a national formulary.

3-Such agency could facilitate the use of "outcomes-based risk sharing agreements" to cover expensive drugs faster.

4-Giving more money to drug companies for expensive drugs will not necessarily translate into more research and development for orphan drugs.

5-Spending more on public research, development and manufacturing, based on an open-science model, could be more effective at developing new breakthrough treatments at affordable prices.

6-A better regulation of patented drug prices through the Patent Act, as proposed in the new PMPRB guidelines, could be very effective at preserving private incentives in developing new drugs for rare diseases while making these drugs more affordable for all Canadians.

Hopefully, all these considerations will be taken into account by Health Canada.