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House of Commons' Standing Committee on Health: Development of a National Pharmacare Program

May 4, 2016

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Overview

Canada should implement national pharmacare consistent with the principles outlined in the Pharmacare 2020 report. (Morgan et al. 2015a) The best evidence we have shows that national pharmacare will save approximately \$7 billion and—more importantly—hundreds of lives each year. (Morgan et al. 2015b)

The issue, then, is *not* whether to institute national pharmacare, but *how*. For, even though the need for national pharmacare has been plain since the 1964 Hall Commission, the landscape of medicine and pharmaceuticals has changed dramatically since then.

Of particular note is the pharmaceutical industry's growing interest in drugs that target relatively small patient populations—often described interchangeably as 'orphan', 'niche', or 'specialty' drugs—in the pursuit of so-called 'personalized' or 'precision medicine.'

This brief focuses specifically on the challenges posed by the push for more personalized medicine. These challenges serve to underscore why national pharmacare is needed, and define some of its essential features.

Context: Recent Shifts in Pharmaceutical R&D

The basic idea behind personalized medicine is to use genetic and other kinds of information about a person's molecular make-up (sometimes referred collectively as 'biomarkers') to develop therapies that are more safe and/or effective for that person. Well-known examples of such targeted therapies include trastuzumab (Herceptin), a therapy used to treat roughly 25-30% of breast cancer patients; imatinib (Gleevec), a treatment for a subset of chronic myeloid leukemia patients; ivacaftor (Kalydeco), a therapy currently indicated for about 5% of cystic fibrosis patients with a particular genetic profile; and, sofosbuvir (Solvadi) and ledipasvir/sofosbuvir (Harvoni), two treatments used to treat particular genetic variants of the hepatitis C virus.

Following the Human Genome Project and other large-scale research initiatives, a wealth of information now exists about a wide variety of molecular biomarkers, disease risk, prognosis, and treatment response. Yet, the clinical significance of many biomarkers remains unclear. In other words, personalized medicine remains largely aspirational at this stage; nevertheless, researchers and pharmaceutical companies are increasingly integrating biomarkers into drug discovery and development.

Two other trends in pharmaceutical research and development (R&D) are worth noting. First, pharmaceutical companies are also moving steadily toward more complex therapies, whether in the form of larger biologics such as monoclonal antibodies (both Herceptin and Gleevec fall in this category), drugs with companion diagnostic tests, or combination therapies, for example, ivacaftor was recently approved to treat another subset of cystic fibrosis patients in conjunction with lumacaftor. Due to their increasing complexity, these products are often referred to as 'specialty drugs'.

Second, pharmaceutical companies are allocating a growing proportion of their resources toward diseases that are relatively rare within a given population. (Karst 2016) In jurisdictions with policies meant to encourage that kind of activity, these therapies are referred to as 'orphan drugs'. In 2015, nearly half (21 of 45) of the novel drugs that were approved by the United States Food and Drug Administration fell into that category. (FDA 2016)

Behind these intersecting R&D trends lies a new pharmaceutical business model. (Gibson and Lemmens 2014) Companies are shifting their focus to more complex drugs, at times incorporating biomarkers, and often targeting rare diseases, because the costs of developing them are generally less than drugs intended for larger patient populations; the path to market tends to be faster; the volume and quality of the evidence required to gain market approval tends to be less because the patients suffering from a given rare disease are, by definition, few in number; and, once approved, such drugs typically encounter little to no competition in the marketplace, positioning companies to negotiate premium prices with payers. (Meekings et al. 2012)

Unlike the United States (US), Europe and other jurisdictions, Canada does not presently have a streamlined regulatory pathway to the market and extra incentives for companies to develop for drugs for rare diseases. (Panju and Bell 2010; Herder 2013) That has not stopped drug manufacturers from seeking access to the Canadian market, however. Between 1997-2013, 74% of the drugs targeting rare diseases that entered the US market were also available in Canada, up from 63% 1983-1996. (Herder and Krahn 2016)

The federal government promised that it would introduce an orphan drug policy in 2012. (Government of Canada 2012) Assuming the government follows through on that promise soon, coupled with the industry's growing focus on rare diseases, it is likely that the number of specialty drugs approved for sale in Canada will continue to rise.

Already, specialty drugs account for a growing proportion of public health care spending on pharmaceuticals in Canada. (Morgan et al. 2013a) They are also amongst the biggest cost drivers of private drug plans in recent years. (PMPRB 2016) Given their growing cost, specialty drugs present a key policy challenge that both make the case for national pharmacare, and should inform how it is designed.

Why National Pharmacare? Kalydeco as an Example

Canada's current patchwork of regulators, health technology assessment agencies, and public and private payers is ill-equipped to grapple with industry's shift toward more

personalized medicine and specialty drugs. The drug ivacaftor (brandname: Kalydeco), manufactured by Vertex Pharmaceuticals, powerfully illustrates this problem.

Kalydeco was initially approved by Health Canada in 2012 as a sufficiently safe and effective treatment for a sub-group of cystic fibrosis patients with a particular genetic profile. It did so largely on the basis of a research study involving 161 patients (more traditional research studies typically involve 6,000-7,000 patients). Vertex set the price at roughly \$300,000 per patient per year. The Canadian Agency for Drugs and Technologies in Health (CADTH) subsequently reviewed the evidence about the safety and effectiveness of the drug in light of Vertex's price, ultimately recommending against governments listing the drug on provincial formularies absent a "substantial reduction in price". (CADTH 2013) News coverage of isolated patients in one province after another who would benefit from the drug followed, putting pressure on provincial payers to pay for Kalydeco despite CADTH's recommendation. One province, Nova Scotia, stated they might have to take a look at funding at the stated price given the small number of eligible patients (7) in the province. Negotiations across the country stalled. Eventually, the Pan Canadian Pricing Alliance (PCPA) and Vertex reached a confidential agreement on the drug's price, resulting in coverage of Kalydeco for eligible cystic fibrosis patients across the country. Meanwhile, the evidence surrounding Kalydeco continues to evolve, with one study suggesting the drug's effect was "roughly equal to that of three far-lower-tech, universally applicable treatments." (Interlandi 2016).

Kalydeco illustrates at least four flaws in our current system of drug coverage.

First, there is a major "data divide" between the level of evidence that Health Canada requires to grant market approval, and the level of evidence that CADTH and payers require to list drugs on provincial formularies. (Flood and Dyke 2012) This divide is exacerbated by specialty drugs like Kalydeco, which are typically granted market approval on the basis of limited evidence due to the small number of patients affected by the disease. As more specialty drugs are developed, conventional approaches to assessing drug safety, efficacy, and cost-effectiveness will be increasingly challenged.

Second, our multi-payer system gives rise to a "politics of division" that compromises evidence-based decision-making about which drugs to pay for. Drug companies are adept at pitting provinces against one another, both directly, by charging lower prices to larger provinces under terms of strict confidentiality (Morgan et al. 2013b), and indirectly, through patient groups that pressure larger and smaller provinces alike to provide coverage. (Weeks 2016) The Canadian Organization for Rare Disorders has already proven to be an influential patient group. (Embrett 2014)

Third, even when public payers band together as the PCPA did in the case of Kalydeco, it is doubtful that the negotiated price is optimal. Public drug plans represented by the PCPA only account for approximately 40% of total drug coverage in Canada. (Morgan et al. 2015a) The PCPA thus has weaker negotiating power than a national formulary representing all Canadians.

Fourth, the evidence and reasoning behind the agreement negotiated by the PCPA is not publicly known; like provincial product listing agreements, the PCPA's agreement with Vertex is bound by strict terms of confidentiality. It is therefore impossible to

assess the PCPA's decision-making, or inform how future drug manufacturers set drug prices.

Improving Canada's Institutional Capacity: Four Essential Features

National pharmacare is not a panacea. However, a national formulary offers the strongest policy response to the challenges posed by high-priced specialty drugs like Kalydeco by increasing Canada's negotiating power, and provided it is well designed. The following four features are essential to national pharmacare:

1. Well-defined information sharing channels

Personalized, specialty drugs, especially those targeting small populations, tend to be approved for sale on the basis of limited evidence. As a result, the studies conducted prior to market approval run a higher risk of "identifying benefits that are not real or missing risks that are." (Kesselheim and Avorn 2011: 1546). A national formulary must be extremely attentive to the evidentiary profiles of drugs as they evolve following market approval.

To that end, the formulary should establish well-defined information sharing channels with Health Canada and other key actors. The regulator frequently grants only *conditional* market approvals for specialty drugs; that is, companies are expected to carry out further research about the safety and effectiveness of the drug *after* it is on the market. Health Canada has poorly enforced these post-market study requirements to date (Law 2014; Lexchin 2007), but its authority to do so and share such information with other governmental bodies was strengthened with the passage of "Vanessa's Law" in 2014.¹ A national formulary should take advantage of these new powers and ensure it has timely access to this body of post-market drug information, as well as evidence compiled by other independent entities such as the Drug Safety and Effectiveness Network (DSEN), the Canadian Network for Observational Drug Effect Studies (CNODES), and Cochrane Canada.

2. Nimble, value-based approach to drug reimbursement

At present, drug coverage decisions are typically 'yes or no' in nature and difficult to undo once made. Given the high costs of many specialty drugs, it is essential that a national formulary aim to negotiate more nimble product listing agreements that reflect the limitations of the evidence base about such drugs at the time of the decision while also striving to achieve maximum value-for-money.

One approach is to tie drug coverage to ongoing evidence development sponsored by the drug's manufacturer (Hutton et al. 2007); this can usefully piggy-back on any post-market study requirements imposed by Health Canada at the time of market approval. Another, still more sophisticated option are "performance-based risk-sharing arrangements" or "PBRsAs" (Garrison et al. 2013; Gibson and Lemmens 2014) In some cases, PBRsAs limit payment to when benefits are actually observed in patients. In other cases, the payment amount varies depending on the stage of the disease and the

¹ See sections 21.1, 21.7, 21.31, and 21.32 of the *Food and Drugs Act*, R.S.C. 1985, c. F-27.

drug's corresponding health benefit. For instance, a payer agrees to pay the full price for the hepatitis C drug Solvadi for stage 4 patients—where the health benefit of the drug stands to be the greatest—but a lesser price for stage 1, 2, and 3 patients.

It is possible to enter into PBRsAs without universal pharmacare in place. However, many payers (both public and private) in Canada lack the capacity to collect and analyze evidence about a drug, as it evolves, or decipher how best to maximize therapeutic value-for-money in pricing negotiations. In principle, a national formulary should have greater institutional capacity to collect and analyze data in order to make more fine-tuned, performance-based drug coverage decisions that seek to maximize value-for-money on a population level.

3. Strong Institutional independence

The national formulary should be given the authority to make binding decisions about drug coverage, and—critically—to modify those decisions as the evidence surrounding a given drug shifts over time. Without that authority, 'coverage with evidence development' and PBRsAs are at risk of becoming means for drug companies to secure lasting payment for drugs of questionable benefit. (Gibson and Lemmens 2014)

Under the current system, CADTH can only make recommendations, which provincial payers are free to ignore. This has paved the way for drug companies and patient groups to train their attention on provincial payers, in turn, politicizing drug coverage decisions. Granting the national formulary the authority to make binding determinations about when and how to pay for and—if warranted by the evolving evidence about a drug's safety or effectiveness—to stop paying for drugs, will help depoliticize drug coverage decisions.

While an arm's length formulary may defeat the politics of division that companies and patient groups currently deploy to pressure provinces and territories into covering treatments for rare diseases, it is likely to increase the risk of industry capture, particularly, through the work of patient groups. A national formulary, then, should not only be arm's length from government, but also as free from industry influence as possible. Those charged with making drug coverage decisions must not simply disclose real or potential conflicts of interest; instead, they should be conflict-free. To the extent patient groups are invited to appear before the formulary as part of its decision-making process, those groups should be required to fully disclose their relationships with drug manufacturers.

4. Transparent decision-making

Kalydeco's price was negotiated in secret. This practice undermines both the public accountability of drug coverage decisions as well as any attempt to hold manufacturers to performance-based drug pricing. Instead, drug pricing, particularly in the realm of specialty drugs for rare diseases, is largely a function of what the market will bear, not the costs incurring in developing the drug, much less the actual impact of the drug on patients' health. (O'Sullivan et al. 2013; Grootendorst et al. 2011; Herder 2016) The national formulary should therefore be legally required to publish its drug coverage decisions and the reasons behind them. This need not necessarily extend to the actual

negotiated price; international cooperation may be necessary to achieve meaningful transparency around drug pricing. But it should include an assessment of the drug's R&D costs, the drug's demonstrated and potential health benefits, and the target population's treatment options; as well as how those considerations informed the details of the product listing agreement. By making that level of reasoning transparent in its decisions, over time, the national formulary can refine and encourage an evidence-based approach to drug coverage.

Conclusion

To date, the health related benefits of personalized medicine have been "equivocal". (Interlandi 2016) There is ongoing debate about the value of many of these new interventions. Yet, there is little doubt that industry's focus on specialty drugs will continue to grow because of the higher prices these treatments typically command.

Given these trends in pharmaceutical research and pricing, instituting national pharmacare is a necessity. Cost containment is unlikely unless Canada's full negotiating power is consolidated into a national formulary.

Personalized medicine's laudable goal is to enable more *precise* decision-making about which drugs to use; it remains a work in progress. National pharmacare, designed as an evidence-based, independent, and transparent institution, has the potential to radically improve Canada's capacity to make more *precise* decisions about which drugs to pay for; it is an imperative as more and more high cost specialty drugs of uncertain benefit enter the market.

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