COMMENTARY

We need a "made in Canada" orphan drug framework

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Canada is one of the few developed countries without a regulatory framework for orphan drugs.[1] Orphan drugs are medications used for the treatment of rare or orphan diseases, which are defined by their low prevalence (fewer than one in 2000 people) and serious, life-limiting nature.[2] Although each individual disease is uncommon, rare diseases are collectively estimated to affect 1 in 12 Canadians.[2] Among the 6000 to 8000 rare diseases identified, most are genetically inherited and have onset during childhood. The emergence of novel therapies for pediatric neuromuscular disorders has emphasized the need for a rare disease framework in this country.

The United States passed an Orphan Drug Act in 1983 with the goal of encouraging drug research and development for the treatment of rare and "neglected" diseases.[3] Given the rarity of each disease, this legislation created incentives for companies who were otherwise not expected to recoup the cost of research, clinical trials and regulatory approval. Five broad categories of incentives were created: tax credits, priority reviews, research grants, protocol assistance and market exclusivity.[3] More than 25 jurisdictions now have their own orphan drug frameworks, including Japan (in 1993), Australia (in 1998) and the European Union (in 2000).[1,3] Health Canada initially rejected the idea of an orphan drug policy in 1997, but in 2012, announced plans to develop a framework.[3] Five years later, Canadians with rare diseases continue to wait for details.

Canadians need an orphan drug framework to ensure timely access to safe and effective treatments. Given the absence of such a framework in Canada, it is important to consider what obstacles may stand in the way. One reason may be complacency arising from Health Canada's Special Access Programme, which enables Canadians to access drugs for clinical purposes even when these drugs lack approval in Canada. The Special Access Programme has worked well for cheaper, generic medications in cases where industry has not sought approval to the smaller Canadian market. However, the Special Access Programme is an ineffective pathway for accessing newer, costly drugs. Drugs that lack Health Canada approval do not have a Drug Identification Number, which prevents reimbursement of their cost by most provincial and private insurance providers. Another reason for developing a framework may stem from Canada's proximity to the US. Canada has benefited from drug research and development stimulated by the US Orphan Drug Act while simultaneously facing increasing challenges associated with the high costs of such treatments.

KEY POINTS

- Orphan drugs are used to treat rare or "orphan" diseases; rare diseases as a group affect 1 in 12 Canadians.
- Canada is one of the few developed nations that does not have an orphan drug framework.
- A Canadian orphan drug framework would ensure access to safe and effective therapies for patients with rare diseases.

Affordability and accessibility are concerns shared by patients, physicians and governments. Provincial health care budgets are allocating a growing proportion of health care budgets to pharmaceutical costs.[4] The increasing number of costly orphan drugs threatens to further strain these budgets. For example, Spinraza (nusinersen) was recently approved by Health Canada for the treatment of spinal muscular atrophy. It is currently moving through the CADTH Common Drug Review process, which will make recommendations regarding coverage and price. Although Spinraza has been shown to be effective at improving strength and function in children with spinal muscular atrophy type 1 and 2,[5] it is expected to carry a high price tag in Canada. In 2016, the US Food and Drug Administration (FDA) approved Spinraza at a cost of US$500 000 (Can$625 000) per patient per year.[6] Such high costs will not be sustainable in an environment where personalized and gene mutation–specific therapies are on the rise.

Repurposing of "old" drugs or extending patent protection by drug reformulation (known as "evergreening") can also lead to inflated prices. The US FDA recently granted orphan drug designation to Emflaza (deflazacort). This corticosteroid is used to prolong independent ambulation in boys with Duchenne muscular dystrophy and has been available in Europe for decades. Deflazacort is currently obtained through Health Canada's Special Access Programme and is supplied by Sanofi-Aventis for about Can$500 per patient per year. After Marathon Pharmaceuticals obtained US Orphan Drug Approval for Emflaza, it announced an annual cost of

US$89 000 (Can$110 000) per patient per year. Subsequently, Marathon sold the rights of Emflaza to PTC Therapeutics, which announced a price reduction to US$35 000 (Can$43 000) per patient per year,[7] still a substantial inflation in price. Emflaza must be seen as a cautionary tale. The granting of orphan drug designation to repurposed medication is perceived by many to lie outside the initial purpose of the US Orphan Drug Act. Although there are costs associated with applying for drug approval and manufacturing pharmaceutical-grade products, the established safety and efficacy for these drugs do not require the same investment that is necessary for novel orphan drugs.

Corporate incentives have been the cornerstone of policies aimed at stimulating research and development for orphan drugs. This has had the desired effect of stimulating research on rare diseases, as the percentage approval of new orphan drugs is now increasing at a faster rate than that of nonorphan drugs.[8] Many have proven to be highly profitable, with some reaching annual global sales in excess of US$1 billion.[9] Some governments have recommended that a proportion of sales be "clawed back" in cases where orphan drugs become highly profitable, as this is outside the early vision of such orphan drug policies; namely, to reward companies that were potentially unable to recoup their financial costs. Tax credits, an incentive offered by many countries (including Canada), may favour large, well-established companies and fail to provide the same stimulus for smaller companies or investigators.[3] Some have advocated for the elimination of tax credits in favour of a grant program in which the recipient would be required to adhere to a "price cap" for their orphan drug should it be brought successfully to market.[10] Canada must consider such novel incentives.

Because clinical trials are carried out across Canada in highly specialized academic teaching hospitals, an alternative to tax credits could be for the Canadian government to invest in establishing a specialized network of clinical trial sites and engage Canadian physicians. Health Canada has expressed a desire to construct a regulatory framework that would span the life cycle of a drug.[11] A Canadian orphan drug framework could ensure that the government engages early with industry in the orphan drug development process. The government must invest in the existing infrastructure in our academic centres. Partnering with academic institutions would have the potential benefit of stimulating investigator-initiated studies (not only industry-sponsored studies). Moreover, by investing in such infrastructure during the "infancy" of a given drug's development, the Canadian government could potentially negotiate price caps or price reductions.[10] However, drug approval pathways and designations must differentiate genuine novel therapies from repurposed or rebranded drugs.

We believe that it is feasible and necessary for Canada to implement an orphan drug framework. It must involve consultation with patients and families with rare diseases, clinicians, clinician-investigators and industry representatives. It should consider existing strengths of Canadian infrastructure and devise novel incentives for drug development and regulatory approval that extend beyond tax credits and high prices. Canadians with rare diseases deserve access to safe and effective therapies that, increasingly, cannot be obtained through the existing Health Canada Special Access Programme. As physicians who care for children with rare diseases, we encourage the Government of Canada to fulfill its 2012 commitment and develop a "made in Canada" orphan drug framework that will balance short-term accessibility with long-term financial sustainability.

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