

Policy alternatives for treatments for rare diseases

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The small market for drugs used to treat rare diseases often makes the drugs extremely expensive. Consequently, many pharmaceutical companies may stop manufacturing these drugs or may not initiate research and development into new therapies. Moving these drugs from bench to bedside requires a partnership among pharmaceutical companies, the clinical community — including patients — and the federal government. Government involvement is arguably the most important, because it provides the structure necessary to link all parties. In stark contrast to other developed nations, and despite the fact that the numbers of rare diseases and people affected continue to increase,¹ Canada does not have a policy framework that connects the three groups and therefore functions with a piecemeal approach. On May 7, 2008, Canada's Parliament passed Bill M-426 calling for the development of a national approach to funding for drugs to treat rare diseases (Box 1).² The motion now awaits approval by the Senate.

In this paper, we examine elements of drug policies for rare diseases that are being used successfully in other nations and could inform a Canadian approach. The analysis of each is based on several factors, including breadth of implementation, key advantages, level of success and the overall impact on the delivery of drugs for treating rare diseases.

Current state

The history of Canada's policy for treating rare diseases is limited.³ At the federal level, the former Emergency Drug Release Program (initiated in 1993) approved and released essential drugs, provided no other treatments were available for a condition.⁴ A physician could request in writing that, with the approval of Health Canada, a pharmaceutical company be authorized to sell or give a precise amount of a drug that had yet to be approved for marketing or sale. In the late 1990s, this program was succeeded by the Special Access Program, which added that practitioners must agree to monitor outcomes of the drug therapy, particularly any suspected adverse reactions.⁵ A 1997 Health Canada report advised against a new drug policy for rare diseases, arguing that it would be "very limited and minimally useful" and that the usual drug approval process outlined in the Food and Drugs Act and its regulations were sufficient.⁶ Among provincial governments, Ontario alone has several programs that reimburse patients for the costs of treatment for rare diseases, such as Gaucher disease.⁷ Parliament's bill aims to address this fragmented system.

Key points

- Canada lacks a policy framework for drugs for treating rare diseases, but it can learn from other countries.
- A population proportion threshold is needed to define rare diseases in Canada, and patient registries can be used to track the progression of disease and related effects.
- Legislation is needed to incent drug development and reimburse patients for costs of drugs for rare diseases.
- An alternative approach to economic evaluation should be grounded in the rule of rescue.
- The framework must be a federal imperative and funded appropriately.

Short-term alternatives

An overview of frameworks applied in the United States, European Union, Japan and Australia reveals elements that can be incorporated into Canadian policy. Two elements can be developed in the short term: defining rare diseases and developing patient registries to track clinical characteristics of a disease, health interventions and health outcomes.

Defining rare diseases

All of the jurisdictions assessed use a discrete population figure or measure of incidence to determine whether a disease is rare (Table 1⁸⁻¹³); this is invariably linked to population. Australia, which has a smaller population than the other nations, defines a rare disorder as one that affects fewer than 2000 people, whereas the United States uses a threshold of 200 000.⁸ It can be argued that such a discrete measure fails to account for changes in population over time; for example, the US population has grown markedly since 1983, when its policy framework was developed.

A more reliable approach to establishing a definition could be to extend Badyal's classification of the drugs for rare diseases to the diseases themselves.¹⁴ Although not formally used in another jurisdiction, the classification considers three essential factors: location, levels of rarity and "study-ability."

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Box 1: The Bell Motion (M-426), the federal private member's bill for the development of a national funding approach for drugs for rare diseases²

In the opinion of the House, the government should respond specifically to the challenges faced by Canadians with rare diseases and disorders, in collaboration with provinces and territories and stakeholders by:

- Examine options for defining serious rare diseases;
- Examine options, including the possible creation of a specific fund, to improve access to rare disease treatments, building on the recent work undertaken by federal and provincial/territorial governments under the National Pharmaceuticals Strategy;
- Consider establishing a multi-stakeholder advisory body, including the Common Drug Review, treaters and patients, to recommend treatment access for life-threatening or serious rare disorders, based on scientific standards and social values;
- Explore options to consider national and international expert advice in developing criteria for treating patients based on scientific evidence and patient impact, and to link these activities with ongoing post-market monitoring of real world drug safety and effectiveness;
- Consider options to encourage research and development into treatments for rare diseases and other unmet health needs;
- Consider internationally accepted standards for conduct of clinical trials in rare disorders appropriate for the challenges inherent to very small patient populations;
- Consider how Health Canada's work on a progressive licensing framework could provide appropriate support to the design of clinical trials for very small patient populations and appropriate review of evidence submitted from these trials; and,
- Report the progress accomplished to the House within 12 months.

Diseases have varying levels of prevalence in different regions. Hepatocellular carcinoma, for instance, is highly prevalent in China (incidence of 95.7/100 000 people) but is relatively uncommon in Canada (3.6/100 000 people).^{15,16} There are also varying levels of rarity ranging, informally, from "rare" to "ultra-rare."¹⁷ Hepatocellular carcinoma may be considered rare, whereas gastrointestinal stromal tumours, with an incidence of 0.0001/100 000 people, could potentially be considered ultra-rare.¹⁸ Such distinctions may have important implications in funding decisions.

Related to the degree of rareness is "study-ability" — that is, whether the prevalence of a disease lends itself to clinical trials and studies. Herein we informally categorize diseases and medications to treat them as "unstudied" or "unstudiable." Unstudied may refer to a newly discovered disease for which drugs have not yet been put through clinical trials. Unstudiable means that the degree of rarity of a disease may make it exceedingly difficult to accrue a statistically sufficient number of patients to participate in a clinical trial.¹⁹

The definitions of rarity can be used for more than decision-making about funding for treatment. They can also be applied to more direct financial policy, such as tax incentives for drug development or deductions on personal income tax.³

Canada would be well served to develop a population threshold or prevalence criterion to determine rarity, just as other nations with frameworks have adopted strict operational definitions (Table 1). A proportionate measure with consistent nomenclature (incidence or prevalence) eliminates ambiguity in establishing rarity and allows more strict classification of diseases and their treatments. This dynamic classification also allows for changes in the prevalence of disease based on regular assessment of epidemiologic data. Comparisons of prevalence of disease among jurisdictions could help identify unstudyable conditions. Establishing such a criterion can guide policy-making for research and development as well as for drug funding.

Patient registries

Several of the jurisdictions we studied use patient registries when establishing drug policy for rare diseases. These robust databases allow monitoring of disease progression, effects of treatment and outcomes.²⁰ They also help to track patients' health and recruit patients for clinical trials; most important, the registries supplement data from traditional clinical trials to determine patient safety, and efficacy and side effects of drug treatment.

Adverse effects from drugs for many common diseases have been detected only during postmarketing surveillance because the initial trials were insufficiently robust to detect harm or because the adverse effects were only discernible after a longer follow-up period.^{21–23} These issues are amplified when considering drug treatment for rare diseases because of the small number of patients and the severity of the diseases. Close follow-up may lead to earlier recognition of potential harm.²⁴

There are many examples of patient registries. For example, Friedreich's Ataxia Research Alliance brings together researchers, clinicians and patients, and supports and informs clinical trials.²⁵ Similarly, France's observatoire on Gaucher disease has collected clinical data on the effects of drug treatment from 107 patients.^{26,27}

Canada's universal health coverage and its sophisticated use of administrative health care databases favours the widespread development of patient registries to track the progression of rare diseases. The Rare Diseases Clinical Research Network in the United States looks to improve the traditional practice of creating registries for individual diseases. By combining 10 large research consortia, the network promotes wide-scale exchange of information, recruitment of patients and performance of clinical trials for as many rare diseases as possible.²⁸ While Canada is in the initial stages of developing a framework, it may want to consider partnering with this US network to support the development of clinical trials and unify the various independent registries that are emerging across the country.

Long-term alternatives

The two most critical long-term steps to structuring a framework are the development of legislation for drugs to treat rare diseases and the implementation of alternative methods of economic evaluation.

Legislation for drug treatment

Government policy for funding of drugs to treat rare diseases requires two aspects: provision of incentives to pharmaceutical companies to develop new treatments, and reimbursement to patients who need expensive drugs.

Three initiatives are found in countries whose policies provide incentives to pharmaceutical companies to develop new drugs for rare diseases:

- offer tax incentives for research and development;
- offer an expedited process for patent application and marketing exclusivity for the the company's products (particularly important to making a profit when costs of production are substantial);²⁹ and
- offer technical assistance — to develop the drugs and ensure that they meet the requisite safety requirements, thereby expediting official listing of the drug and use by patients.

This type of legislation is most effective when pharmaceutical companies are actively pursuing therapies for rare diseases. Canada may want to use the approach of Australia, where drugs that have received approval in other countries (particularly by the US Food and Drug Administration) are approved quickly and made available in drug plans.¹

Some argue that the current rewards for drug creation trump the need for incentive legislation, citing the case of eculizumab (for paroxysmal nocturnal hemoglobinuria).³⁰ This therapy costs about Can\$400 000 per patient per year, and with a Canadian prevalence of this condition of about 2000 patients, this would amount to roughly one billion dollars annually. This is an exceptional case, but does warrant consideration. In 2003, DiMasi and colleagues²⁹ estimated the cost of bringing a drug to market at US\$802 million (in 2000 dollars). They note that in most instances the manufacturers of drugs (that are less expensive and treat diseases with lower prevalence) are unable to recover the investment annually, as they would with eculizumab. The financial risk is compounded when acceptance risk is considered. This is the risk of the drug not being accepted into drug plans. If this is the case, the number

Table 1: Overview of drug legislation for rare diseases in international jurisdictions

Region/ country	Criteria for defining rare disease, population (%) ^{8,9}	No. of designated orphan drugs (effective date)	No. of drugs approved* (effective date)	Legislation (supervising body) ¹⁰	Elements of drug legislation for rare diseases ^{9,10}				
					Tax incentives	Fast-tracking of drug evaluation	Marketing exclusivity (yr)	Technical assistance to obtain approval	Other
Australia	≤ 2000 (0.01)	180 (2010) ¹¹	62 (2010) ¹¹	Australian Orphan Drugs Program (1997) (Therapeutic Goods Administration)	No	Yes	Yes (5)	Yes	Applications reconsidered every 12 months
European Union	5/10 000† (0.05)	664 (2010) ¹²	51 (2010) ¹²	Regulation No. 141/2000 (2000) (European Medicines Evaluation Agency)	Yes	Yes	Yes (10)	Yes	Not applicable
Japan	≤ 50 000 (0.04)	167 (2004) ¹⁰	95 (2004) ¹⁰	Orphan Drug Regulation (1993) (Ministry of Health, Labour and Welfare)	Yes	Yes	Yes (10)	Yes	Partial reimbursement of development costs Extended registration validity period
United States	≤ 200 000 (0.07)	2194 (2010) ¹³	350 (2010) ¹³	Orphan Drug Act (1983) (Food and Drug Administration)	Yes	Yes	Yes (7)	Yes	Not applicable

*This may also be defined as the number of orphan drug marketing authorizations.

†Measure of incidence.

of patients capable of paying the high cost of drugs dwindles, making it more difficult to recover costs. Finally, as Joppi and colleagues³¹ have confirmed, there remains a paucity of drug manufacturers willing to produce drugs for rare diseases, highlighting further the need for incentives.

Few countries, including Canada, have reimbursement programs for patients. A case study for such a program can be found in Ontario, where patients with Gaucher disease receive drug reimbursement linked to the severity of the disease and socio-economic status.⁷ The federal bill to investigate reimbursement programs warrants further consideration and consultation with other jurisdictions.³²

Alternative economic evaluation

Drugs to treat rare diseases are very expensive, because of small demand and high production costs. From an industry perspective, the small number of patients with rare diseases makes it difficult to justify the direct and opportunity costs of extensive research and development. If the drug therapy does make it to market, it comes at a sizeable cost to the patient, government or funding agency. Governments commonly establish thresholds for approving drugs based on cost per quality-adjusted life year, and drugs for rare diseases almost always exceed them.^{33,34} By definition, drugs for rare diseases lack the broad bases of clinical evidence that are available for drugs for more common ailments, which makes economic evaluation difficult.

We advocate for an economic measure rooted in the rule of rescue: the imperative that, in the absence of alternative treatment, patients with life-threatening diseases should receive therapy irrespective of cost.³⁵ Rule of rescue seeks to explain why expensive missions are waged to save, for example, a single sailor lost at sea. In the context of treatment for rare diseases, this rule would allow public funding of expensive drugs that could potentially help a very small number of Canadians. Opponents of the rule characterize it merely as a perceived moral duty with little functional scope. However, the rule highlights the key ethical issue inherent in any discussion of public health care: equitable treatment for all. The rule of rescue has been used in Ontario⁷ and Oregon.³⁶

Federal funding should be allocated to drugs for rare diseases to ensure that they compete with one another, not with a broader group of drugs. A detailed budget impact analysis for each drug would allow responsible planning given scarce and limited resources. It would also help to prioritize programs and model future costs to better understand funding ramifications and create sustainable reimbursement platforms. Frequent reviews and updates would also aid policy-making. Alternatively, drugs for rare diseases could be absorbed into the budget for all prescription medications, as they are in England.¹⁷ However, this approach would lead to inconsistency because the same mechanism for funding would be applied to drugs that are approved by different methods.

Knowledge gaps and future direction

Much is required to establish a policy framework for drugs for rare diseases in developed countries. Most

important, it must be recognized that rare diseases and their drug treatments are sufficiently different to require a distinct framework and funding mechanism. Only then can guidelines be developed to distinguish among and define rare diseases. A population proportion threshold based on clinical data are also necessary, because distinctions among rare diseases may have implications for funding and resource allocation; the thresholds can also provide vital epidemiologic data to support moving forward with framework development.

Second, there is a need to investigate and pilot feasible alternatives to the cost per quality-adjusted life year as a model for economic evaluation. Achieving fair health care for this population requires increased accessibility to effective treatment. This approach should account for the rarity of the disease and economic cost, while considering the legislated incentives that may be provided to drug developers. Detailed analyses on the impact on budget are an essential element of this new process.

Developing and implementing such a framework must be a federal priority to ensure consistent, comparable coverage in all provinces. The competing demands for Canada's limited health care funding point to the need for funds and resources earmarked for treating rare diseases. The framework and federal funding must be closely linked so the provinces are not forced to bear the costs of another initiative. Such a model is in contrast to the federal government's approach to treatments for Fabry disease, which lacks a planned fiscal structure and is already mired in disagreement over the treatment's clinical effectiveness; it has recently resulted in the cancellation of a clinical trial commissioned by the federal government.³⁷

Earmarked allocation of funds and resources, however, raises the question of prioritization. Best practice considers the "accountability for reasonableness" framework,³⁸ which uses four conditions to prioritize scarce health care resources fairly:

- publicity (limit-setting decisions and their rationale must be accessible by the public);
- relevance (decisions must be based on relevant information and principles);
- appeals (a mechanism must exist to challenge decisions and revise them in light of new information); and
- enforcement (voluntary and public regulation of the process is required to ensure that the conditions are met).

The strength of the framework lies in how it links political decision-making with democratic deliberation, thereby granting legitimacy and acceptance to the ultimate outcome. Policy-makers may find alternative or additional sources of funding by providing incentives to pharmaceutical companies to reduce the cost of treatments. Partnerships with national foundations and research networks may also be fostered to build funds from other sources (e.g., private and corporate donors) to be distributed to patients according to the severity of the disease and their socio-economic status. These alternatives demand further study, as do approaches for integrating reimbursement programs into drug legislation for treating rare diseases.

Challenges to implementation

Understandably, a number of challenges must be addressed prior to the implementation of any recommendations. First, the limited number of patients makes it difficult to develop a strong evidentiary base for drug efficacy, and the high cost of treatment increases the expectations of the drug's effectiveness. This disconnect between high costs and imprecise estimates of effect has likely contributed to the rejection of listing treatments for rare diseases by the Common Drug Review.³³ For this reason, we advocate for the broadening of clinical trial criteria for drugs that fall within the prescribed classification scheme, as well as the forms of allowable evidence for consideration in assessing drug safety, including surrogate outcomes. This suggestion reflects the reality of the types of clinical trials that can be conducted with this population. This is not meant, however, to suggest that these drugs should be held to a lower safety or quality standard; rather, there should be greater flexibility in the forms and/or quantity of data made available for assessment.

There have similarly been concerns over the safety of drugs for rare diseases. While a broad-scale investigation of a range of these products has not been conducted, studies of individual drugs, like oral methyl naltrexone³⁹ continue to ensure adherence to fundamental safety standards. Additionally, as Haffner notes, because most rare diseases are serious or life-threatening, patients are willing to accept a higher level of risk.⁴⁰ However, it is also necessary to recognize that because the number of patients using these drugs is limited, the same may be true of their safety profiles. Still, as we advocate, a registry would be the best method to assess for adverse events, particularly if these occur in the longer-term after most clinical trials have ended.

Any discussion of drugs for rare diseases would be incomplete without a mention of ethics and equality. As mentioned, any economic evaluation should be grounded in the rule of rescue, and we have advocated for the use of the accountability for reasonableness prioritization framework. At the base of both is the decision to employ a utilitarian view of health care provision. Although not easy, it is within the government's mandate to take actions that benefit the majority of Canadians. To some, this may suggest that all drugs are not treated fairly; for those for whom these drugs are the final lifeline, it is a necessity. This is consistent with a recent report from Ontario's Citizens' Council.⁴¹

Conclusion

The many issues surrounding drug treatment for rare diseases create challenges to developing a comprehensive federal policy. The rarity of these conditions demands special consideration so that patients receive treatment equitable to that given to patients with more common disorders. Elements of drug policies in other developed countries can inform and help to create a national framework. It is time for Canada to take bold and decisive steps to develop a nationwide and federally financed approach to drug treatment for rare diseases that ensures adequate health care for all Canadians.

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