Federal Funding for Expensive Drugs for Rare Diseases: How Do We Pick and Choose?

Financement fédéral pour les médicaments onéreux pour les maladies rares : comment choisir?

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Abstract
The number of expensive drugs for rare diseases (EDRDs) approved by Health Canada and their contribution to healthcare costs have been rapidly increasing. The federal government has announced a three-year funding commitment of $1.4 billion for EDRDs, but principles need to be developed for how that funding will be allocated, especially in cases where insufficient data are available to guide decision making. Here, we review the role of evidence quality in making choices and draw on the experience from other countries to put forward five principles about how the money should be spent.

Résumé
Le nombre de médicaments onéreux pour les maladies rares (MOMR) approuvés par Santé Canada et leur contribution aux coûts des soins de santé ont rapidement augmenté. Le gouvernement fédéral a annoncé un engagement de financement triennal de 1,4 milliard de

dollars pour les MOMR, mais il reste à élaborer les principes sur la façon dont ces fonds seront alloués, surtout dans les cas où les données disponibles sont insuffisantes pour orienter la prise de décisions. Ici, nous examinons le rôle de la qualité des données dans les choix et nous nous appuyons sur l'expérience d'autres pays pour proposer cinq principes sur la façon de dépenser l'argent.

Introduction

Expensive drugs for rare diseases (EDRDs) are an exploding subset of health expenditures with rapid increases in the number of such drugs approved by Health Canada and their share of total Canadian drug spending (PMPRB 2022). Expensive drugs are those with "estimated treatment costs exceeding $100,000 per year for non-oncology drugs or $7,500 per 28 days for oncology drugs" (PMPRB 2022: 38). The definition of a "rare disease" used by both the European Medicines Agency and the Canadian Organization for Rare Disorders is one affecting five or fewer in 10,000 people (Health Canada 2021).

Canada does not have a formal EDRDs policy despite a decades-long debate on the need for a national orphan drug policy (ODP) but it compares favourably with some countries with ODPs on how many of these drugs come to market and how fast. For example, Australia has had an ODP since 1997, but a higher percentage of orphan drugs approved in the US are marketed in Canada than in Australia and are marketed at the same time with similar lengths of time spent in regulatory processes (Lexchin and Moroz 2020).

However, having drugs approved for the Canadian market does not help patients unless the drugs are reimbursed. Delays and discrepancies in listing marketed drugs on provincial formularies are a challenge for patients. In March 2023, the government acted on this point with a three-year plan to spend over $1.5 billion on the National Strategy for Drugs for Rare Diseases (Health Canada 2023). Most of the money ($1.4 billion) is targeted to a cost-sharing program with the provinces to provide coverage of a common set of new and emerging drugs, while also enabling provinces and territories to enhance coverage for existing drugs and supporting improvements in screening and diagnostics (Health Canada 2023). However, that level of federal funding will leave gaps in coverage even for highly effective drugs. For example, five EDRDs that were rated as offering substantial improvements and/or breakthrough status had total annual Canadian sales of over $1.2 billion (Table 1) (PMPRB 2022). Federal funding would not cover even these five drugs, let alone any upcoming drugs. Therefore, we need principles to decide which drugs to cover.

International Experience Can Inform the Use of Federal Funds

The federal funds for EDRDs are unique given that healthcare services in Canada are traditionally provided by the provinces, with drug manufacturers having to navigate separate systems of the 13 provinces and territories. Other countries have experience that could be used to inform the use of the federal funds. In most jurisdictions, EDRDs are treated in

TABLE 1. Top 10 EDRDs: Sales and therapeutic ratings

Generic name	Brand name	Sales (2021, $ millions)	PMPRB therapeutic rating[¶]	Indications
Lenalidomide	Revlimid	537.7	Breakthrough*	**Multiple myelomas in combination with dexamethasone,** myelodysplastic syndromes
Pembrolizumab	Keytruda	525.7	Slight to none[†]	**Melanoma**, Hodgkin lymphoma, B-cell lymphoma, urothelial carcinoma, bladder cancer, lung cancer, renal cell carcinoma, colorectal cancer, endometrial carcinoma, squamous cell cancer, gastric adenocarcinoma, esophageal carcinoma, breast cancer, cervical cancer
Ibrutinib	Imbruvica	349.5	Substantial[‡]	**Chronic lymphocytic lymphoma**, mantle cell lymphoma, Waldenström's macroglobulinemia, graft versus host disease
Daratumumab	Darzalex	254.3	Moderate[§]	**Multiple myelomas**, amyloidosis
Nivolumab	Opdivo	249.6	Slight to none	**Melanoma**, Hodgkin lymphoma, colorectal cancer, urothelial cancer, non-small cell carcinoma, mesothelioma, renal cell carcinoma, squamous cell cancer, gastroesophageal cancer
Eculizumab	Soliris	180.1	Breakthrough	**Paroxysmal nocturnal hemoglobinuria**, atypical hemolytic uremic syndrome, myasthenia gravis, neuromyelitis optica spectrum disorder
Osimertinib	Tagrisso	178.4	Moderate	**Non-small cell lung cancer**
Nusinersen sodium	Spinraza	97.2	Breakthrough	**Spinal muscular atrophy**
Durvalumab	Imfinzi	92.1	Slight to none	**Urothelial carcinoma**, non-small cell lung cancer, small cell lung cancer, biliary tract cancer
Ipilimumab	Yervoy	75.2	Substantial	**Melanoma**, colorectal cancer, renal cell cancer, non-small cell lung cancer, mesothelioma, esophageal carcinoma

EDRDs = expensive drugs for rare diseases; PMPRB = Patented Medicine Prices Review Board.
Initial approved indication in bold.

¶ Therapeutic rating based on initial approved indication.

* First drug to be sold in Canada that effectively treats a particular illness or effectively addresses a particular indication.

† Relative to other drug products sold in Canada, provides slight or no improvement in therapeutic effects or provides slight or no savings to the Canadian healthcare system and/or to patients and/or caregivers.

‡ Relative to other drug products sold in Canada, provides substantial improvement in therapeutic effects or provides substantial savings to the Canadian healthcare system and/or to patients and/or caregivers.

§ Relative to other drug products sold in Canada, provides moderate improvement in therapeutic effects or provides moderate savings to the Canadian healthcare system and/or to patients and/or caregivers.

Source: PMPRB 2022.

the same manner as other medicines, but some countries have established separate mechanisms. In Australia, drugs may be considered through a separate Life Saving Drugs Program. In the UK, the National Institute for Health and Care Excellence has a program that evaluates the benefits and costs of a limited number of drugs for very rare conditions. France, Germany and Sweden allow validated surrogate endpoints as measures of clinical efficacy/effectiveness for EDRDs. Scotland makes EDRDs available through a Patient Access Scheme for up to three years while further evidence on their effectiveness is generated. After that evidence is available, the drug undergoes a reassessment that includes a Patient and Clinician Engagement meeting (Stafinski et al. 2022).

Beyond just receiving submissions from individual patients and patient groups, Germany, England and Scotland have formal patient involvement teams within review bodies (Stafinski et al. 2022). In Germany, topic-specific patient representatives are appointed to committees for a single review. Generally, there is only indirect patient involvement in the development of terms and conditions of contractual agreements that tie reimbursement to evidence generation (Stafinski et al. 2022).

How Is Canada Responding to the Challenges of EDRDs?

To deal with situations where there is both an unmet need and insufficient data at the time of market entry to determine the benefits of a drug, two new programs were launched in September 2023. The Canadian Agency for Drugs and Technologies in Health (CADTH, now Canada's Drug Agency) created a new category known as "time-limited recommendations (TLRs)" to facilitate early access to drugs for patients with rare diseases (Canada's Drug Agency 2023b). To be eligible, drugs must have "robust" evidence-development plans to fill the gaps identified at the time of health technology assessment (HTA). Importantly, the manufacturer of the drug seeking TLRs must commit to having its drug reassessed within a defined timeline, even if this means the recommendation may be withdrawn. Drugs with a TLR have price negotiations through a second new temporary access program offered by the pan-Canadian Pharmaceutical Alliance where risk sharing is part of the negotiation process (pCPA 2023). Decisions about how robust evidence should be defined will need to be contextualized to reflect, among other things, the severity and long-term consequences of the condition and the availability of other therapies. One approach to doing so could involve the use of a national expert panel as suggested in a discussion paper released in 2021 (Health Canada 2021) and could draw on a national data system that incorporates both already existing disease registries (Inform Rare n.d.) and new ones that provide comprehensive and consistent information about how treatments for rare diseases are used by Canadians and how they are working.

What Is the Role of Evidence Quality in Making Choices?

High-quality evidence should be the gold standard for making therapeutic choices, but

pivotal studies for rare diseases that form the basis for regulatory approval often exhibit methodological flaws; for example, they lack quality-of-life measures, may not be blinded and depend on surrogate endpoints (Lexchin 2023). Some of these deficiencies are inherent in trials for rare diseases where small patient numbers limit power. If there is no existing therapy to give to a control group, enrolling a placebo group may be considered unethical for debilitating or fatal diseases. Finally, the limited understanding of the relationship of biomarkers to disease pathology may decrease study validity (Shah et al. 2021).

Real-world evidence (RWE) can complement other types of studies (Sirrs et al. 2023), but the time needed to generate data leaves patients waiting for options. CADTH recently developed recommendations for the use of RWE but it will take time to assess the impacts of these new guidelines (Canada's Drug Agency 2023a). Regardless of when the evidence is available (pre- or post-market), ultimately decision makers need evidence that a drug provides a clinically meaningful improvement in the quality and/or quantity of life. Judgements about what is clinically meaningful should be made with input from experts in the disease area plus people with lived experience of the disease.

What Principles Can Be Used to Aid Decision Making Around Federal Funds for EDRDs?

We should not pay for drugs that do not work. As with all drugs, the therapeutic value of EDRDs is variable. Out of 46 drugs that had a therapeutic evaluation by the Patented Medicine Prices Review Board between 2010 and 2019, 22 were rated as offering slight to no therapeutic benefit compared with existing drugs, while only 10 were considered substantial improvements or breakthroughs (NPDUIS 2022). For those EDRDs where high-quality clinical evidence was generated prior to market entry, separate routes for reimbursement are not needed. The first principle we suggest is that in these cases, instead of using federal funds, existing HTA infrastructure should inform value-based price negotiations as the basis for listing on provincial/territorial formularies when evidence sufficient for HTA is available prior to market access. Federal funds should only be considered for use in situations where there are convincing reasons why high-quality evidence is not possible prior to market entry (e.g., in rare patient subsets of a given disease), rather than as a means for manufacturers to avoid doing a rigorous pre-market clinical trial.

Second, new drugs for diseases where good therapeutic alternatives are already available in Canada should not be unconditionally reimbursed until such time as high-quality data about clinically relevant outcomes are available. With some EDRDs, only limited knowledge about their effectiveness (Kennedy-Martin et al. 2015) and safety (Singh and Loke 2012) are available at the time of market entry. Risk-sharing agreements are one tool for regulators to balance the challenge of timely access to drugs when considerable uncertainties remain at the time of market access and have been used in Australia mainly for oncology products (Tuffaha and Scuffham 2018). For this reason, we suggest that federal EDRD funds should

be prioritized for those drugs where manufacturers are amenable to meaningful risk-sharing agreements. These agreements can help with common challenges faced by payors such as patient subsets not included in clinical trials. For example, elexacaftor/tezacaftor/ivacaftor (Trikafta) is a breakthrough therapy for cystic fibrosis (CF) approved in Canada for patients who have at least one copy of the most common CF mutation, p.Phe508del (CADTH 2021). Some, but not all, of the rare CF mutations may respond to therapy and trials of treatment for patients with rare mutations could be negotiated on a pay-for-performance basis. Those manufacturers who do not have enough confidence in their drug to put it to the test in risk-sharing agreements should not benefit from the federal EDRD funds.

It follows then that the third principle underlying the use of the federal EDRD funds should be a willingness by the manufacturer to participate in post-market generation of high-quality evidence. This principle does carry some risk for manufacturers in that funding should be withdrawn if post-market trials fail to provide convincing evidence of the drug's value or if the trials fail to be completed. Adherence to this principle will also require changes in Canada's regulatory structures to mandate the reassessment of drugs across their life cycle and, more importantly, to act on the results of this reassessment.

The TLR process specifies that the manufacturer must have a plan for a phase III clinical trial but simply having a plan for a phase III trial should not be sufficient. Not all phase III trials are of similar quality – one worrisome trend has been the explosion of clinical trial structures such as single-arm trials (which are more subject to confounders than to traditional randomized controlled trials) in the oncology field (Agrawal et al. 2023). The excuse for these lower-quality studies is the size of the rare disease population, but size does not guarantee quality – even large patient datasets must be combined with good clinical trial design or else the trial simply becomes a marketing tool. Research in rare diseases requires international collaboration to gain sufficient patient numbers and such collaboration has been recently prioritized by the Canadian Institutes of Health Research (CIHR 2023). We suggest that the fourth principle is that the quality of the evidence-generation plan should be used to choose drug candidates that can take advantage of the federal EDRD funds, thus prioritizing those drugs whose plans optimize clinical trial design and maximize patient numbers through international collaborations where necessary.

Perhaps the most important and final principle around the use of federal EDRD funds is that of fairness. Spending on EDRDs has far outpaced spending in other areas of healthcare, effectively shifting limited healthcare resources from common diseases toward rare diseases (Sirrs et al. 2023). The high opportunity costs for EDRDs make it just as important to engage the public as a stakeholder as it is to engage patients, healthcare providers, manufacturers, regulators and payors. Engaging the public requires transparency around the decision-making processes, opportunity costs and the results of reassessment of the drug across its life cycle. Such transparency has largely been lacking for EDRDs (Sirrs et al. 2023), and moves to enhance transparency are complicated by Canada's proximity to the lucrative

US drug market. Transparency does not mean that governments and manufacturers have to release specific details of negotiated agreements. However, the broad strokes of those agreements can be made public, as they are in other jurisdictions such as the UK (NICE 2019). Drugs where manufacturers are unwilling to allow for this degree of transparency should not be considered as candidates for the funds.

Summary

In order to spend the $1.4 billion in federal money responsibly for EDRDs, drawing on the evidence that we reviewed here and the practices in other countries, we recommend the following five principles:

1. Drugs where high-quality evidence is available prior to market entry should be handled through the existing infrastructure with the federal funds reserved for drugs where the development of high-quality evidence is not possible prior to market entry.
2. Risk-sharing funding agreements should be in place until high-quality evidence showing clinically relevant outcomes is available.
3. Manufacturers should be willing to participate in meaningful evidence-generation with the understanding that if the results of post-market trials do not provide convincing evidence of value, funding will be withdrawn.
4. The quality of the research plan should be used to prioritize candidates for federal funding.
5. There must be meaningful public engagement in order to promote transparency in decision making and all parties have to accept the need for transparency.

Disclaimer

The views expressed in this article are those of the authors and not official positions of their affiliated institutions.

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