Expensive Drugs for Rare Diseases: "Canada, We Have a Problem Here"

INTRODUCTION

Joel Lexchin, MSc, MD
Professor Emeritus
School of Health Policy and Management
York University
Associate Professor
Faculty of Medicine
University of Toronto
Toronto, ON

Introduction

This issue of *Healthcare Papers* on expensive drugs for rare diseases (EDRDs) is very timely. According to the recently released Patented Medicine Prices Review Board's 2021 annual report, EDRDs have gone from 1.7% of pharmaceutical expenditures in 2012 to 12.2% in 2021, with a compound annual growth rate between 2012 and 2021 of 31.7% compared to 6.0% for all prescription medicines (PMPRB 2022).

Although EDRDs are prescribed for a wide variety of diseases, three-quarters of all EDRD spending in 2021 was for oncology products, with sales of lenalidomide (Revlimid) coming in at $537.7 million (PMPRB 2022). At the same time, a recent report from the United States did not find a link between measures of benefit and the price for drugs that treat cancer. Oncology drugs approved on the basis of overall survival improvement had a lower median price than drugs approved using surrogate end points such as progression-free survival or overall response rate (Miljković et al. 2022). This finding about the (non-)relationship between benefits and pricing is especially concerning since (based on my unpublished research) 52 of the 61 new oncology drugs approved in Canada between 2015 and 2020 used surrogate outcomes. Based on a European study, it is unlikely that there will be definitive clinical evidence for the large majority of those drugs. Of the 39 oncology medicines approved by the European Medicines Agency without any proven benefit on meaningful survival or improved quality of life, only six had generated that evidence after a minimum follow-up of 3.3 years (Davis et al. 2017).

To paraphrase the communication between the Apollo 13 astronauts and the NASA Mission Control Center: "Canada, we have a problem here". This problem and what to do about it are tackled by Sirrs and colleagues (2023a) and the various commentators in this issue.

How to Pay for EDRDs

In the 1980s and the 1990s, pharmaceutical companies' goal was to bring to market drugs for common chronic diseases in industrialized countries and sell them at a modest price – the "blockbuster" model, where the aim was to generate $1 billion per year in revenue. But as the patents on these lucrative drugs, such as Lipitor, started to expire, and realizing that much of the low-hanging fruit had been picked, the model switched to a "niche-buster" one. As Sirrs et al. (2023a) point out, this move was stimulated by the passage of the *Orphan Drug Act* (1983) in the US and similar legislation in other countries and the rapid expansion in the use of biologic therapies.

These new therapies, geared to treating rare diseases (those occurring in less than five per 10,000 people), cost less to develop because clinical trials were conducted on smaller populations (Jayasundara et al. 2019), but the drugs were priced based on what the market would bear, making them affordable only through private or, more likely, public insurance. Moreover, competition could not be counted on to bring prices down as with generic drugs. Biosimilars are slow to arrive on the Canadian market and do not exist for many biologics, and when they do, they often do not offer substantial price savings (PMPRB 2019).

How should we pay for these drugs? Sirrs et al. (2023a) advocate only paying for drugs that provide value for money and are supported by evidence. They say that "[r]ather than pay initial prices based on their hypothetical maximum benefit, we should create a more realistic risk-sharing model that sets prices more reasonably until additional data validate the hype" (Sirrs et al. 2023a: 23). As part of that process of gathering additional data, they promote the use of real-world evidence (RWE), possibly making it mandatory for patients to contribute their data in order to receive funding. Stevenson (2023) picks up on the use of RWE that would employ a pan-Canadian approach to capture data and points out that this will require "effective collaboration among healthcare professionals, beneficiaries of [drugs for rare diseases], pharmaceutical companies and government funders" (p. 30). Douglas (2023) agrees that 13 individual post-marketing regimes, one for each province and territory, is "unrealistic, inefficient and pointless given patient numbers for individual rare diseases" (p. 68).

One way of generating these data is through the use of managed access agreements, which, as described by McPhail and Bubela (2023), use "a variety of price and evidence generation mechanisms to support value-based decision making" (p. 59). Depending on the evidence, prices could either be raised or lowered. Hollis (2023) is the only commentator to directly address the importance of using development costs in setting prices. He points out that basing reimbursement on the average cost of new drug development has already been implemented in the United Kingdom's antimicrobial subscription pilot. He also uses the "p-word," making the point that drugs should be priced so as not to generate excessive profits for the seller.

However, none of the papers in this collection recommend requiring companies to open their books and justify their development costs. Nor does anyone suggest that given the public input into drug development, either directly or indirectly, some of the value of the drug should accrue to the public in the form of lower prices.

Ethics and EDRDs

Of course, price is not the only major issue in deciding about coverage for EDRDs. Ethics should always be front and centre in decision

making. Typically, large sums of money are being spent on single individuals when this money could also be directed to, in the words of Sirrs et al. (2023a: 21), "maximize the overall benefit society receives from public investments," bringing to light the tension between social utility and justice. To Sirrs et al. (2023a), this tension should be resolved through procedural justice – that is, making decisions in a way that inspires "faith in those affected, who will be inclined to follow the decision even if it goes against their personal interest" (p. 22). Stevenson (2023) also strongly endorses "embed[ding] the principles of procedural fairness and enhanced transparency throughout the decision-making process – that is, be specific, fair and transparent throughout" (p. 31).

Sirrs et al. (2023a) mention the "rule of rescue" as one of the key ethical issues that needs to be considered when we think about how EDRDs are going to be funded. In brief, the rule of rescue can be defined as an ethical imperative to save individual lives even when money might be more efficiently spent to prevent deaths in the larger population. Keating questions whether the rational basis for resource allocation, recommended by Sirrs et al. and Stevenson, is sufficient to allay concerns about how money is allocated: "Citizens are not rational actors;" therefore, "[t]he perception of the legitimacy of the conclusions of a deliberation, even when held under ideal conditions of speech, on such sensitive issues will always remain at risk" (Keating 2023: 42–43).

Evidence behind EDRDs

Ethics and financing are both predicated on the evidence that EDRDs offer more benefits than harms, and all the authors, in one way or another, acknowledge this. However, the evidence behind EDRDs can sometimes be slim, at least in the initial stages of their use. In our haste to rush these medications to patients, we are willing to tolerate limitations, often unavoidable, in clinical trials such as single-arm studies, surrogate end points and lack of randomization and blinding, which limit our knowledge about harms and benefits (Kesselheim et al. 2011). In the case of oncology drugs, Jenei and Gyawali (2023) note, "Most of these studies do not collect relevant patient-centred outcomes, such as overall survival and quality of life. Furthermore, inappropriate subgroup analyses and high occurrence of crossover can bias study results" (p. 47). The result is that the evidentiary basis for drugs for rare cancers is far below that expected for more common cancers.

Acquiring more evidence about EDRDs can be time consuming. It took a decade to accumulate the data to show that agalsidase alfa or agalsidase beta, used in treating Fabry disease, had limited effect on quality of life and progression to end-organ damage. This modest effectiveness meant that the cost per year free of end-organ damage was millions of euros (Rombach et al. 2013). Slow follow-ups after EDRDs are licensed are not uncommon, and even when the post-market studies fail to show effectiveness, drugs can still remain on the market (Gyawali et al. 2021; Lexchin 2021).

RWE is likely to be increasingly important in evidence collection. RWE can be extremely valuable, especially as a signal of unexpected side effects, but the use of RWE is expanding beyond just the detection of rare harms. Like all forms of evidence, quality is what counts, and RWE can have significant limitations, "including conflicts with the funding source, fragmentation of patient populations among competing registries and incomplete data capture" (Sirrs et al. 2023a: 19). Recognition of these quality issues is behind the Canadian Agency for Drugs and Technologies in Health's initiative to develop a Canadian action plan to optimize the

process for the integration of RWE into both regulatory and reimbursement decision making in Canada (Tadrous et al. 2020).

Evidence is used by multiple stakeholders in arguing for and against the approval and reimbursement of EDRDs. In the past decade, patient groups have come to the fore as one of the more prominent stakeholders in these decisions. Sirrs et al. (2023a) only mention them in passing; therefore, the contribution of Batt (2023) is especially welcome. She describes Canada's patient advocacy landscape and contrasts how different groups shape the landscape around EDRDs. As the federal government phased out the funding of patient groups in the 1990s, many of them turned to industry for funding, as Batt describes. Receipt of industry funding does not automatically correlate with an orientation in favour of the goals of drug companies, but at present, only a minority of patient groups have policies for how to deal with their interactions with industry (Lexchin et al. 2022). Patients' and patient groups' input based on their own experiences can be extremely valuable in making decisions about EDRDs, but we need to be sure of their independence.

How Does Canada Move Forward?

Although orphan drug legislation exists in multiple jurisdictions, including the US, the European Union, Australia, Singapore and Israel, Canada has been hemming and hawing about legislation for over 25 years without coming to a final decision. But even without laws, as a small market (about 2% of the global market for prescription drugs), Canada is heavily affected by what happens elsewhere, especially in the US. Over 70% of the orphan drugs approved by the US Food and Drug Administration are also approved by Health Canada (Lexchin and Moroz 2020). US approval standards are also mirrored in Canada, and Health Canada is extremely reluctant to step out of line with larger jurisdictions, such as the US and the European Medicines Agency, for fear that companies will not market drugs here.

In their response to the commentators, Sirrs et al. (2023b) outline actions that can be taken by all of the stakeholders: federal, provincial/territorial governments, healthcare providers, patients, the public and manufacturers. Douglas (2023) complements what Sirrs et al. (2023b) say by pointing us in the direction of what is happening in Europe for lessons that Canada could look at adapting. But he also notes the challenges in transposing other countries' experiences onto the Canadian context. Instead, a novel approach that Douglas proposes is the emerging interdisciplinary framework of social pharmaceutical innovation (SPIN): "SPIN offers a rethinking of the entire innovation ecosystem and seeks to understand, evaluate and intervene in alternative approaches to pharmaceutical research, development and deployment throughout the life cycle of treatments" (Douglas 2023: 70).

Conclusion

The financial, ethical and evidentiary issues around EDRDs are entangled in a Gordian knot, and it will only be possible to untangle the knot if all three are tackled together; otherwise, the question of how to deal with EDRDs will continue to vex Canadian healthcare. The authors of the papers that form this issue of *Healthcare Papers* have done an excellent job of bringing to light many of the issues that policy makers will need to deal with as they go forward. It has been my distinct pleasure to work with all of them and to be involved in guiding this issue to its conclusion.

References

Batt, S. 2023. Competing Values, Competing Claims: Diversity among Patient Advocates Who Intervene to Shape Policies on Drugs for Rare Diseases. *Healthcare Papers* 21(1): 52–58. doi:10.12927/hcpap.2023.27995

Davis, C., H. Naci, E. Gurpinar, E. Poplavska, A. Pinto and A. Aggarwal. 2017. Availability of Evidence of Benefits on Overall Survival and Quality of Life of Cancer Drugs Approved by European Medicines Agency: Retrospective Cohort Study of Drug Approvals 2009–13. *BMJ* 359: j4530. doi:10.1136/bmj.j4530.

Douglas, C. 2023. International Experiences and Made-in-Canada "Social Pharmaceutical Innovations" as Responses to Challenges Facing Drugs for Rare Diseases. *Healthcare Papers* 21(1): 66–72. doi:10.12927/hcpap.2023.27993

Gyawali, B., B. Rome and A. Kesselheim. 2021. Regulatory and Clinical Consequences of Negative Confirmatory Trials of Accelerated Approval Cancer Drugs: Retrospective Observational Study. *BMJ* 374: n1959. doi:10.1136/*BMJ*.n1959.

Hollis, A. 2023. High Prices for High Profits? *Healthcare Papers* 21(1): 34–37. doi:10.12927/hcpap.2023.27998.

Jayasundara, K., A. Hollis, M. Krahn, M. Mamdani, J. Hoch and P. Grootendorst. 2019. Estimating the Clinical Cost of Drug Development for Orphan versus Non-Orphan Drugs. *Orphanet Journal of Rare Diseases* 14(1): 12. doi:10.1186/s13023-018-0990-4.

Jenei, K. and B. Gyawali. 2023. Expensive Drug Prices for Rare Cancers: Are Patients Truly Benefitting? *Healthcare Papers* 21(1): 44–51. doi:10.12927/hcpap.2023.27996.

Keating, B. 2023. What Procedural Ethics Can Learn from the Quest for Moral Justification for the "Rule of Rescue." *Healthcare Papers* 21(1): 38–43. doi:10.12927/hcpap.2023.27997.

Kesselheim, A.S., J.A. Myers and J. Avorn. 2011. Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer. *JAMA* 305(22): 2320–26. doi:10.1001/jama.2011.769.

Lexchin, J. 2021. A Comparison of the Food and Drug Administration's and Health Canada's Regulatory Decisions about Failed Confirmatory Trials for Oncology Drugs: An Observational Study. *Journal of Pharmaceutical Policy and Practice* 14: 93. doi:10.1186/s40545-021-00375-y.

Lexchin, J., S. Batt, D. Goldberg and A. Shnier. 2022. National Patient Groups in Canada and Their Disclosure of Relationships with Pharmaceutical Companies: A Cross-Sectional Study. *BMJ Open* 12(3): e055287. doi:10.1136/bmjopen-2021-055287.

Lexchin, J. and N. Moroz. 2020. Does an Orphan Drug Policy Make a Difference in Access? A Comparison of Canada and Australia. *International Journal of Health Services* 50(2): 166–72. doi:10.1177/0020731419886526.

McPhail, M. and T. Bubela. 2023. Can Managed Access Agreements Mitigate Evidentiary, Economic and Ethical Issues with Access to Expensive Drugs for Rare Diseases in the Canadian Context? *Healthcare Papers* 21(1): 59–65. doi:10.12927/hcpap.2023.27994.

Miljković, M.D., J.E. Tuia, T. Olivier, A. Haslam and V. Prasad. 2022. Association between US Drug Price and Measures of Efficacy for Oncology Drugs Approved by the US Food and Drug Administration from 2015 to 2020. *JAMA Internal Medicine* 182(12): 1319–20. doi:10.1001/jamainternmed.2022.4924.

Orphan Drug Act. Public Law 97-414—JAN. 4, 1983, 96 Stat. 2049. Retrieved November 28, 2022. <https://www.govinfo.gov/content/pkg/STATUTE-96/pdf/STATUTE-96-Pg2049.pdf>.

Patented Medicine Prices Review Board (PMPRB). 2019, April. Biosimilars in Canada: Current Environment and Future Opportunity. Retrieved December 12, 2022. <http://www.pmprb-cepmb.gc.ca/CMFiles/News%20and%20Events/Speeches/biosimilars-april2019-en.pdf>.

Patented Medicine Prices Review Board (PMPRB). 2022. Annual Report 2021. Retrieved December 12, 2022. <https://www.canada.ca/content/dam/pmprb-cepmb/documents/reports-and-studies/annual-report/2021/2021-Annual-Report-en.pdf>.

Rombach, S.M., C.E.M. Hollak, G.E. Linthorst and M.G.W. Dijkgraaf. 2013. Cost-Effectiveness of Enzyme Replacement Therapy for Fabry Disease. *Orphanet Journal of Rare Diseases* 19(8): 29. doi:10.1186/1750-1172-8-29.

Sirrs, S., H. Anderson, B. Jiwani, L.D. Lynd, E. Lun, B. Nakagawa et al. 2023a. Expensive Drugs for Rare Diseases in Canada: What Value and at What Cost? *Healthcare Papers* 21(1): 10–26. doi:10.12927/hcpap.2023.27000.

Sirrs, S., H. Anderson, B. Jiwani, E. Lun, B. Nakagawa, D. Regier et al. 2023b. Expensive Drugs for Rare Diseases in Canada: Time for Action Everywhere and by Everyone. *Healthcare Papers* 21(1): 74–80. doi:10.12927/hcpap.2023.27992.

Stevenson, H. 2023. Specific, Fair and Transparent: A Canadian Process for Funding Drugs for Rare Diseases. *Healthcare Papers* 21(1): 28–33. doi:10.12927/hcpap.2023.27999.

Tadrous, M., T. Ahuja, B. Ghosh and R. Kropp. 2020. Developing a Canadian Real-World Evidence Action Plan across the Drug Life Cycle. *Healthcare Policy* 15(4): 41–47. doi:10.12927/hcpol.2020.26225.