Canadian Organization for Rare Disorders

# An Open Letter to Canada's Health Ministers re: Rare Disease Drugs

This is an open letter to all of the Heath Ministers in Canada from the Canadian Organization for Rare Disorders, presenting a simple and elegant solution to providing appropriate, timely, and sustainable access to therapies for rare disease patients and other targeted patient subgroups living with more common conditions.

Innovative therapies, including drugs for rare diseases, have been much maligned as threats to affordable drug coverage, but they may actually provide the solution to the ultimate goal of "the right drug to the right patient at the right time and at the right price." In order to use these "small patient population" therapies effectively and cost-effectively, we need to evolve responsive and responsible pathways to manage their use. It is given that not all drugs work for all individuals. It is equally true that some drugs, albeit listed as "open access" on formularies, have demonstrated "more benefits than harms for only slightly more than 50% of the persons tested." So, for many common conditions, nearly half of patients may be prescribed a therapy that is individually suboptimal. Which, of course, is also not cost-effective.

Traditionally, clinicians wishing to prescribe the right medicine and correct dosage would make their best guess (based on clinical guidelines), observe the outcomes, and adjust accordingly, or change therapies. This is not a "common" pattern for rare diseases drugs, in part because knowledge about the disease, the therapy, and patient outcomes may be very limited, and there are few, if any, alternative therapies. In other cases, a "trial-and-error" approach (such as the "double-blind randomized controlled clinical trial") is neither appropriate nor likely to yield illuminating results, since the therapy is designed specifically to address the "cause" of the condition, often a genetic abnormality, and the treatment (replacing a missing enzyme or blocking gene expression) almost always works. This latter scenario also defines "targeted" therapies (aka precision or personalized medicines) that are developed for subtypes of common conditions, often defined by specific genetic abnormalities (for example, gene mutations, changes in the DNA, and over-expression or under-expression of a gene). Again, once the patient is correctly diagnosed through the appropriate genetic and/or other tests, the therapy should work. What may not be certain is whether all patients with the genetic abnormality require therapy, the optimal time for starting therapy, the potential complications of co-morbidities, and the patient preference in considering the benefits versus risks.

A key barrier to optimizing appropriate and timely access is the lack of certainty around "real world" effectiveness, safety and patient timing due, in large part, to small and often short clinical trials. These are, after all, small patient populations often with life-threatening or serious conditions and no other viable treatments where the goal has been to make therapies available, to the broader patient

community, as soon as possible. Unfortunately, the short clinical trials, often using surrogate markers and a very narrowly defined sample to optimize results, is often the bane of the health technology assessors and payers, who are looking for certainty in clinical outcomes, changes in disease status, and/or additional "life years", preferably high-quality ones. This conundrum is a universal challenge, and various jurisdictions, including Canada, have evolved a variety of solutions. So what is the elegant solution that CORD proposes?

In 2014, CORD called for a "managed access" approach to drugs for rare diseases that would address both the urgent unmet needs of patients and the uncertainty of effectiveness and safety of drugs tested with small patient populations. In reality, managed access schemes, defined as "*an approach to providing access to drugs by setting criteria (based on evidence) for starting (such as, disease status, symptoms, previous treatments, co-morbidities, or age), how patients should be monitored while on therapy, and criteria that would indicate the therapy needs to be changed or the patient transitioned to something else*" have been used to introduce rare and targeted therapies for a number of years. For example, managed access schemes (aka as managed entry agreements, coverage with evidence development, or risk sharing schemes) underlie the Canadian Fabry Disease Initiative, Ontario's Drugs for Rare Diseases framework, Cancer Care Ontario's Evidence Building Program, and the first Federal/Provincial/Territorial "Expensive Drugs for Rare Diseases" proposal in 2008 as part of the National Pharmaceutical Strategy.

Currently, a limiting factor to MAS is the "disconnect" between the regulatory review (Health Canada) and all of the review processes (Common Drug Review, panCanadian Oncology Drug Review, Institut national d'excellence en santé et en services sociaux (INESSS), provincial drug reviews, and panCanadian Pharmaceutical Alliance) used to reach a decision whether to reimburse, or not. Similarly, the requirements for data and patient monitoring prior to allowing drugs on the market are mostly nonexistent once the drugs are in general use. The disconnect is driven partly by divergent aspirations: for patients and clinicians, the desire to access therapies matched to individual profiles, offering better efficacy and safety; for developers, managing the complexities and cost of proving targeted therapies for small patient populations; for payers, deciding value for money when drugs are very expensive and evidence highly uncertainly against traditional assessment methods. But that pattern is changing.

Canada's imminent implementation of the Orphan Drug Regulatory Framework, premised on a lifecycle approach to drug approval, offers the opportunity to adopt a continuous evaluation approach that engages all stakeholders, including patients, reviewers, and payers, from the very beginning to define the "value proposition." The collective goal is to define the desired outcomes from the each stakeholder's perspective, set up mechanisms to assure the evidence is collected and analyzed, and to make evolving decisions accordingly (for example, update the guidelines, increase monitoring, liberalize access, or call for changes to the price).

In Europe, countries like Italy and Spain have been using managed access schemes, not exclusively for rare disease drugs, for many years. There have also been pilots

in the UK and the Netherlands. In 2014, the European Medicines Agency announced the first set of drugs to be considered under its pilot "adaptive licensing" project, seeking "to examine whether iterative, 'adaptive' approaches to medicine development and authorisation offer advantages in terms of achieving the best balance between the need for timely patient access with the importance of providing adequate, evolving information on a medicine's benefits and risks." As importantly, the project calls for early engagement of the HTA bodies (under the umbrella of the European Network of HTA, or EUNetHTA), the payers, and the patient organizations to determine the evidence that needs to be generated as well as the "hurdles" to data collection.

Even in the USA, where access and pricing have traditionally been negotiated through market forces, policy makers, publicly administered drug plans, and insurers are looking at a managed "health economics and outcomes research" (HEOR) approach to the reimbursement of precision medicines "when the clinical and/or economic value proposition for the broader patient populations is unfavorable, unclear, or unexceptional" as they seek to "limit coverage of such therapies to subpopulations most likely to benefit."

In Canada, the challenges of implementing managed access schemes have been (successfully) addressed with many of the rare disease drugs currently in use. Rare disease clinics and specialty pharmacies have established patient registries (collecting natural history data along with drug utilization and other patient outcomes) and providing on-going monitoring and assessment, often updating clinical practice guidelines in the process. While recognizing the need for internationally linked MAS and patient registries, as well as international evaluation of outcomes, we suggest that Canada, at this time, take a bold step in implementing MAS as a standard strategy for "innovative targeted therapies." The opportunity comes from Canada's Orphan Drug Regulatory Framework (developed and soon to be implemented) and the recently announced Provincial and Territorial Health Ministers' working group on "evidence-based approaches" to managing rare disease drug therapies. We urge the Working Group to set up pilot MAS projects with rare disease therapies currently seeking reimbursement to develop recommendations based on experience with real drugs and real patients. The Canadian Organization for Rare Diseases has asked that CORD be invited as a member of the working group to ensure the pilots and deliberations are directly informed by patient perspectives. We definitely can afford rare disease drugs. We cannot afford not to make them available. We just need to do right.

Respectfully submitted,

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