Is the current approach to reviewing new drugs condemning the victims of rare diseases to death? A call for a national orphan drug review policy

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Powerful financial incentives created by orphan drug legislation, particularly in the United States,[1] have resulted in the emergence of new, innovative therapies for a number of rare diseases. In Canada, approval for the commercial sale of new drugs is controlled by the Therapeutic Products Directorate of Health Canada, which adjudicates their safety and efficacy on the basis of information provided by the manufacturers. However, many of the new therapies are so expensive that, without financial support from provincial drug plans, access to them is a practical impossibility. For example, the annual cost of the treatment of Fabry disease with agalsidase alfa is over $250 000 per patient per year, depending on the weight of the patient.

The process for reviewing new drugs for the purposes of public reimbursement is designed to ensure that the public is getting its money's worth from its financial support for patients. Once a purely provincial initiative, the process is now sponsored by the federal government as the Common Drug Review (CDR). Administered by the Canadian Coordinating Office on Health Technology Assessment,[2] the CDR may ultimately replace the several provincial processes doing virtually the same job.

The CDR makes its recommendations for reimbursement on the basis of a rigorous evaluation of cost-effectiveness that involves a review of the available clinical evidence and pharmacoeconomic data. This review is undertaken by the Canadian Expert Drug Advisory Committee with input from experienced external and internal reviewers. Although cost is generally well-understood and relatively easy to compute, the evaluation of effectiveness is not, particularly when it is applied to therapies for rare diseases.

These difficulties of evaluation are due in part to the nature of rare diseases. By definition they affect only a few hundred patients at any one time in Canada. The frequency of many of the disorders is so low that it is next to impossible in the short term to gather enough patients to achieve sufficient statistical power to demonstrate significant clinical benefits of a therapy. Moreover, the diseases are often complex and multisystem, and they tend to pursue highly variable clinical courses. It may take years to demonstrate a clear-cut effect of treatment on mortality. Furthermore, if a therapy is evaluated on the basis of a single outcome that only a fraction of patients experience as the primary cause of morbidity, the ability to carry out rigorous clinical trials of therapy is diminished. In many patients, the most common causes of morbidity are inherently difficult to quantify. This is true, for example, of Fabry disease, a lysosomal disorder in which irregular episodes of severe pain are one of the most consistent causes of morbidity.[3] The use of composite outcome measures is compromised by the small number of patients. Because the disorders are rare, few centres will have sufficient long-term experience with affected patients to be able to describe confidently the natural history of the diseases. This further complicates the assessment of new therapies — knowledge of the untreated course of the diseases, in the detail required for the development of clinical trials, is usually incomplete.

Since its inception in September 2003, the CDR has undertaken 34 reviews of 33 new drugs, of which 14 received recommendations for reimbursement. All 14 were for common conditions for which similar drugs are already available (see Tables 1 and 2 available at www.cmaj.ca/cgi/content/full/174/2/189/DC1).[4] In contrast, at least 6 of the 19 new drugs not recommended for reimbursement were developed to treat rare diseases for which no alternative primary treatment exists. The principal reason given for withholding a recommendation for reimbursement was insufficient evidence of significant clinical benefit, in large part because of the reliance on surrogate outcomes for the evaluation of outcomes. In each of the cases involving new drugs for rare diseases, such as Fabry disease, Gaucher disease and mucopolysaccharidosis type I, the reviews commented on the high cost of treatment.

> It is virtually impossible to assess cost-effectiveness of treatments for rare diseases using conventional criteria.

Should Canadian patients be denied access to potentially effective new treatments for formerly untreatable and serious diseases only because it is virtually impossible to evaluate the cost-effectiveness of those treatments using conventional criteria?

One way to deal with the situation would be to modify the review process for rare disease therapies: the infrastructure and resources of the existing CDR would be used, but greater use of surrogate outcomes would be allowed, and industry would be required to support a process of continuing review of clinical outcomes.

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The process would be open to *all* rare disease treatments that are approved by the Therapeutic Products Directorate for use in Canada. This requires that "rare" be defined; most industrialized countries have done this, although the definitions vary considerably. The definition developed for use in Canada would ultimately need to be determined by discussion and consultation between regulatory authorities and medical and epidemiological consultants.

The criteria for approval should be based on efficacy, but using rational surrogate outcome measures if clinical efficacy data are incomplete. The process should include the establishment of management guidelines for the selection of patients who would qualify for reimbursement for therapy. A precedent for this exists with the Gaucher disease-specific treatment programs in Ontario,[5] Alberta and British Columbia.

A central component of the process would be a commitment to ongoing evaluation of patients through registries designed to collect clinical information on patients receiving the new drug (and having all of the appropriate measures to ensure confidentiality). Approval for continued reimbursement could be made conditional on appropriate reporting of patient data by attending physicians. The establishment and maintenance of the necessary registries and the analysis of data would be seen as the responsibility of rare diseases expert committees, which would be composed of internal and external reviewers in relevant fields of medicine, health technology assessment, and epidemiology, and financed primarily by industry. Sufficient data would ultimately be accumulated to permit a more rigorous evaluation of the therapy. Meanwhile, no patient with a rare disease would be denied access to a new, potentially life-saving treatment. Conversely, a therapy might be discovered to be of little or no value, or even harmful, during this closely monitored phase of the process, and support for the treatment withdrawn.

The proposed program would ensure early access to new, potentially beneficial treatments for patients with rare diseases. It also ensures equitable access to therapy for patients with different rare conditions, so that those with diseases lacking influential advocacy groups can also receive new therapies. It takes advantage of existing infrastructure, and it ensures accountability through appropriate monitoring of patients for drug efficacy and safety. It involves industry as an active supporter of monitoring process. Finally, it ensures national uniformity in the use of drugs for the treatment of rare disease. The national scope of the proposed program is consonant with Romanow's Catastrophic Drug Transfer,[6] which will spread the costs and facilitate recruitment of appropriate medical experts for service on review committees.

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