



CANADIAN ORGANIZATION FOR RARE DISORDERS

Canada's Orphan Drug Policy

Learning from the Best

Introduction

Canadians suffering from rare debilitating or life threatening diseases need an Orphan Drug Policy that will assure Canadians with rare diseases have timely affordable access to the best therapies and provide competitive incentives for Canadian-based companies to engage in research and development to bring new therapies to market. This paper discusses the rationale for orphan drug policies and the recommendations for an effective “made-in-Canada” policy.

What is an Orphan Disease?

The designation of “orphan disease” varies depending on the respective country, ranging from a fairly restrictive ratio of 1:9,090 for Australia (or 2,000 affected individuals) to 1:1,333 (or 200,000 potential patient populations) in the United States. In Japan, the prevalence for rare diseases is 1:2,000 (50,000 patients in the population) and in Europe, the legislation applies to diseases with a prevalence rate of 1:2000 (185,000 patients). In Canada, there is no official “orphan disease” status but, based on international standards, could be defined as diseases with a potential patient population of 3,300 (Australian standards) to 22,500 (US definition).

According to the National Institutes of Health, there may be 5,000 to 6,000 rare diseases, about 4,000 of which are genetically based (single-gene mutation). Interestingly, the US FDA allows the orphan designation to be applied to “medically plausible subsets” of diseases, resulting in an increasing number of applications for orphan products to treat types of cancer or respiratory disease. As the application of pharmacogenomics expands, there may be many more “disease subsets” that would fit into this category.

What is an Orphan Drug Policy?

The first national orphan drug policy was introduced on January 4, 1983, when the United States passed the Orphan Drug Act to stimulate research and development of medicines as well as devices to diagnose and treat diseases. Since these diseases are so rare, affecting a small percentage of the population, it does not provide incentives for the pharmaceutical and biotechnology companies to develop orphan drugs. It took ten years for the second country, Japan, to follow with a similar, albeit less generous,

amendment to its drug regulatory and taxation laws. In addition, Australia passed a similar policy in 1999. The policy focused on facilitating market access to drugs that had already received orphan status in the USA and did not provide incentives for Australian R & D.¹ Furthermore, the European Union passed new legislation in 2000 to facilitate the availability and accessibility of orphan drugs. The new legislation granted lower application fees and ten-year market exclusivity, and country-specific research incentives to manufacturers of drugs for rare, life-threatening or serious diseases.

In contrast, Health Canada concluded in November 27, 1996 that there was no need for a specific orphan drug policy. In 1996 the participants concluded that the means to support research or market access for treatments for rare diseases could be accommodated under existing programs.

What Has Been The Impact of Orphan Drug Legislation?

US Orphan Drug Act 1983 (Scientific American, May 2003)

It has been more than 20 years since the US passed the Orphan Drug Act in 1983. The Act was the culmination of years of intense lobbying directed at motivating major pharmaceutical companies to develop therapies (often based on research that had been publicly funded) that were considered to be commercially unprofitable because of high costs to bring the product to market for a very small potential patient population. The key elements of the legislation were research and development of tax incentives amounting to 50% of the clinical costs and seven-year market exclusivity, with additional support in the form of assistance in developing research protocols (with appropriate sample size and endpoints) as well as expedited reviews for market approval.

There are some concerns that the legislation has reaped unintended “windfalls” for some manufacturers. Some drugs, or technologies, that were accorded “orphan” status have gone on to serve larger populations and become highly profitable. Others have remained very expensive for the patient population, despite the support for R & D.

Overall, almost everyone agrees that millions of patients have benefited from Orphan Drug Legislation. The results have “exceeded expectations”, with over 238 orphan designated products brought to market in the USA since legislation (as compared to only 34 in the previous decade) and over 1200 orphan designations awarded. In a 20-year review of the Orphan Drug Act, *Scientific American* concluded,

“Act certainly has its warts, but in a free-market economy, it is the best model devised so far to ensure that those with rare diseases can get the treatments they so desperately need.”²

¹ Australia Government, Department of Health and Ageing, Therapeutic Goods Administration, “Orphan Drug Program Review” online: <http://www.tga.gov.au/docs/html/orphan.htm>. The Therapeutic Goods Administration states that the Australian Orphan Drug Program encourages sponsors to market drugs

¹ Maeder T. The Orphan Drug Backlash. *Scientific American*, May 2003, 81-87.

Japan and Australia Orphan Drug Program

Japan's legislation provides only modest R&D support, does not include a waiver of fees for market approval but does guarantee 10 years market exclusivity. It has resulted in approvals of nearly 100 orphan products in 12 years.

Unlike the USA and Japan, the Australian amendments to the Therapeutic Goods Act in 1989 are directed only toward drugs and do not include R&D incentive. The proposal to provide five-year market exclusivity has not yet been enshrined in legislation. Australian orphan drug legislation is directed at improving the availability of treatments for rare diseases, especially those already marketed in the USA. To that end, it allows for the USA FDA data to be accepted and also ensures "flexibility" in data requirements, as well as waiver of application fees. Moreover, the Australian program specifically addresses the need to make drugs affordable to patients, with some subsidies from the Pharmaceutical Benefits Scheme and discussions with Australian Healthcare Authorities for assistance to patients.

European Parliament of the Regulation on Orphan Medicinal Products

In 2000, the European Union passed new legislation, designating medicinal products as orphans and providing incentives for research, development and marketing of orphan drugs following the recommendations derived from a survey done for the European Parliament.³ Like the previous legislation, orphan drugs were defined as those directed towards rare diseases with very low prevalence or very small total patient populations, with "life-threatening, seriously debilitating, or serious and chronic consequences, and for which there were no other methods of diagnosis or treatment that offered a significant benefit.

A joint Committee for Orphan Medicinal Products (COMP) was established to review applications. The EU legislation offered market exclusivity for 10 years in all countries and lower fees for market authorization; research incentives and other benefits would need to be negotiated on individual country basis.

Unfortunately, the legislation appears to be unable to address the inequality in access across countries. Eurodis (European Organization for Rare Disorders) has cited the lack of transparency in traceability of product availability, despite a mandate for each country to set a price and level of reimbursement within 180 days. A survey of 12 drugs that had received EU authorization by December 2003 found that there was media availability of only 5 drugs, with a range from 0 to 12 drugs available to patients. The aforementioned problems included the following: price disparity, insurance coverage for rare diseases, variations in distribution networks and reimbursement of medical

³Orphan Drugs. STOA Publications, 1999.
http://www.europarl.eu.int/stoa/publi/167780/chap5_en.htm
6/7/05

payments.⁴ They have called for a European Commission consultative committee, consisting of volunteers to evaluate the risk-benefit ratio and propose price brackets agreed with by industry to remove inequities to patient access.⁵

Why Canada needs An Orphan Drug Policy?

Canadians with rare disorders run the risk of being among the last in the developed countries to gain access to new medicines, if at all. In 1997, Health Canada specifically rejected the need for a Canadian Orphan Drug Policy, citing that “means” to assure access to drugs for rare diseases were available to manufacturers within existing legislation.⁶ In particular, Health Canada cited several mechanisms that could be applied to orphan drugs:

- Priority review (“fast tracking”) for treatments deemed first in class for the treatment or diagnosis of serious, life-threatening diseases where there was clinical evidence of important therapeutic gain
- Conditional Approval (NOCC) based on surrogate markers or early trial results with agreement for post-market confirmatory studies
- Reduction of fees for drugs with small market potential
- Access to unapproved drugs through Emergency Drug Release Program and Special Authorization Program.

In particular, Health Canada contends that the mechanisms are sufficient because the majority (63%) of US-approved orphan drugs is approved in Canada (but not necessarily for the same reason). Moreover, Health Canada claims that provision for R & D tax credit already exists under the Scientific Research & Experimental Development Tax Incentive program.

Unfortunately, these mechanisms are not sufficient to insure that Canadian patients with rare diseases will have access to critical and life-saving medicines. There is no motivation for manufacturers to seek market approval and to make these drugs available in Canada. Since Canada does not offer competitive R&D incentives, there will be no Canadian-based pharmaceutical and biotechnological research and development for domestic use or export.

⁴ Eurodis Survey of Orphan Drugs: Availability and Pricing in EU Member States. European Organisation for Rare Disorders. http://www.eurordis.org/article.php3?id_article=487.

⁵ All the orphan drugs worldwide. European Organisation for Rare Disorders, March 2005. http://www.eurordis.org/article.php3?id_article=442.

⁶ Health Canada Drugs Directorate, “Orphan Drug Policy” (January 16, 1997) at 8 online: Health Canada < http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/orphdrug_e.pdf > [“Orphan Drug Policy”].

In addition, orphan drugs should exist outside of the jurisdiction of the Common Drug Review (CDR).

Biotech Canada Proposal

Biotech Canada, the association of biotechnology firms, has called for policy and incentives to assure that Canada will remain a key player in the burgeoning global biotechnology industry. Biotech is also a key partner in addressing global issues such as the genomics, counter-bioterrorism agents, and vaccines for emerging contagious diseases. Canadian researchers need to gain the research and marketing expertise to help broaden the pipeline for new orphan therapies, especially within pharmacogenomics segment mainstream disease markets.

The current Health Canada regulations must be amended to address appropriate trial size, efficacy, and safety benchmarks for small patient populations. The rules for expedited reviews must be clarified for orphan products and, indeed, there is a need for a definition of an “orphan disease.” Biotech Canada has also called for waivers of submission fees for market approval, mutual or unilateral recognition of FDA or European Medicines Evaluation Agency (EMA) regulatory approvals, and federal tax credits competitive with the USA (50% on R&D and 20-year carry-forward). To support a return on investment, Biotech Canada is calling for a ten-year market exclusivity and, important to patient access, federal dedicated funding for orphan products as part of a national catastrophic drug plan.

Made in Canada Solution to Orphan Drug Access

Perhaps the benefit of being one of the last to develop an Orphan Drug Policy allows Canada to incorporate best practices and learn from other countries. In order to effectively serve Canadians with rare diseases, it is important that a Canadian drug policy address not only research and development and regulatory approval but also affordable access and funding for drug coverage. To these ends, a made-in-Canada orphan drug program must address the roles of the federal and provincial or territorial governments,

Provincially based drug plans are not well suited to assuring access to orphan products to all those who need them. Most provincial drug plans provide coverage based on income, age, disability, or a combination of these criteria. Many orphan therapies, while not a costly additional to the total provincial drug budget because of the small numbers of patients, are nevertheless unaffordable by individual patients, regardless of income. For instance the National Gaucher Foundation of Canada had to lobby the provincial governments to fund the drugs Ceredase and Cerezyme for severely afflicted patients. The Ontario government agreed and in 2001 spent \$3.2 million to fund the therapy for 20 patients. This amount, however, pales in comparison with the \$2 billion Ontario was spending on pharmaceuticals at this time.⁷

⁷ Andrew Duffy, “Rare Diseases Troubling Questions” (January 21, 2002) Ottawa Citizen, A10.

While most provinces have “special drug budgets” that provide coverage for all patients with certain types of diseases, these special drug plans are very limited (cystic fibrosis, HIV/AIDS, end-stage dialysis, and organ transplantation). Moreover, because many rare diseases are genetically determined, their prevalence may vary considerably across provinces. This leads to the perception of disproportionate burden of some therapies in some provinces, especially the smaller provinces. For example, most of the 150-300 Canadians with Fabry’s disease, a life threatening disease which costs over \$240,000 a year to treat, live in Nova Scotia.⁸ To assure equitable Canadian access to orphan therapies, a national orphan drug plan, including drug coverage, is essential.

A national orphan drug plan would assist in ensuring that Canadians with rare diseases have equal access to the Canadian health care system. The government has an ethical and moral obligation to formulate an orphan drug plan which ensures that Canadian citizens do not have to choose between death and bankruptcy.

National Orphan Drug Plan

In 2004, the Health Ministers established a Task Force of F/P/T Ministers to create a National Pharmaceuticals Strategy with a report to the Ministers of Health by June 2006 that includes, among other things:

- Drug trial registration designed to accelerate access to breakthrough drugs
- Drug purchasing strategies
- National formulary and catastrophic drug coverage

There must be specific provision for orphan drugs within this strategy, including:⁹

- Tax incentives for R&D that will make Canadian-based companies competitive with those in the USA and other countries
- Market exclusivity for a specified period of time to be facilitate appropriate Return on Investment (ROI)
- Protocol assistance in the design and development of clinical trials suitable for rare diseases and disease subgroups
- Expedited or fast tracked review of drug submissions to both Health Canada and the Common Drug Review
- Assessments for reimbursement (drug plan coverage) that are pre-planned with manufacturers but also with input from clinical experts and patient groups to assure appropriate costs and benefits are included

⁸ Helen Branswell, “Panel urges Ottawa not to cover Fabry drug costs” (November 28, 2004) CTV, online:

http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/1101672761684_7/?hub=Health.

⁹ de Paulsen N. Working Paper: Abandonment or access: Canada’s Orphan Drug Policy. University of Toronto Health Law and Policy Group. 2004.

http://www.law.utoronto.ca/healthlaw/studentpapers_content.html

- Funding for post-market research and patient registry to collect outcomes and safety data
- Catastrophic drug coverage for orphan drugs with deductibles and co-payments that do not limit access for any patient, regardless of income or age
- Requirements for coverage within private drug plans (with no annual or life-time capitation)