



**Forum 3:
Canadian's with Rare Disorders – Assuring
Access to “State of the Art” Diagnoses and
Therapies**

Summary Proceedings

**Tuesday March 20, 2007
8:30 am – 4:30 pm
Le Saint Sulpice Hotel
Montreal, Quebec**

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Welcome and Objectives of Forum

Durhane Wong-Rieger, President of the Canadian Organization for Rare Disorders (CORD), welcomed participants to the third forum on orphan products policy and outlined the meeting objectives. She covered the top line issues discussed at the previous forums and encouraged all stakeholders to attend the First Canadian Conference on Rare Disorders in Ottawa on April 24-25, 2007. Durhane explained that the objective of the summit conference is to achieve a consensus on goals, rationale and direction for Canadian policies on orphan products that (a) assure Canadians with rare disorders have access to new technologies, in concordance with international best practices, within a context of fairness and accountability that promotes safe, effective, and monitored use; and (b) assure Canada is an attractive and competitive environment for researchers and industries seeking to develop new technologies for rare conditions.

Durhane stated that the underlying purpose of all three forums centers on bringing concrete recommendations before government officials in April. In order to make the most of this opportunity, industry needs to be absolutely clear in their suggestions. Durhane argued that Canada must be harmonized with other international jurisdictions that have adopted an orphan product policy. She closed her opening remarks stating, “Policy that clearly defines an arena must include societal values.”

Therapies for Rare Diseases: Unique Impact, Unique Challenges – Geoffrey McDonough

Geoffrey McDonough of Genzyme began his presentation by addressing the difficulty associated with quantifying/demonstrating the impact of a therapy. Notwithstanding these challenges, he illustrated that orphan products have a dramatic impact on patients' lives by halting, and in some cases reversing, disease progression. He pointed out that the patients in question generally suffer from severe, progressive, and life threatening genetic diseases. From an economic standpoint, Geoffrey highlighted that development costs for therapies for rare diseases are not substantially lower than for larger diseases. However, patients with rare diseases have the same right to effective therapies as those with more common diseases. The core of Orphan Drug Regulation consists of non-economic societal values representing a desire to provide equitable access to therapies independent of the rarity of the disease. In his brief description of Health Technology Assessment (HTA) Geoffrey stated that economic considerations represent only a portion of the total assessment process and are not the determining factor.

There exist many obstacles in accessing marketed orphan products such as the time between obtaining the market approval and placing the product on the market, the reimbursement of these products, prescribing physicians' lack of experience concerning the medical benefits of these medicines and the absence of treatment consensus recommendations. According to Geoffrey, sustainable patient access is contingent upon the effective partnering of industry, patient groups and government along with the

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

recognition of the three key components: central reimbursement, clinical expertise and monitoring. Using the Netherlands as a case example, he showed that models for a public-private partnership that support key elements of a sustainable system do exist. In the Netherlands, the orphan drugs steering committee works as the central reimbursement agency, the centre of excellence functions as the clinical expertise, and disease registries operate as the monitoring wing.

In closing, Geoffrey commented on those patients suffering from Ultra-Orphan Diseases (UODs). This population presents unique challenges to the health system due to the complexity of their needs as well as the high cost of their therapies. Geoffrey stated that sustainable patient access to innovative therapies for UODs can often be achieved through a central reimbursement mechanism and comprehensive HTA. Creative public-private partnerships can yield guidelines, centers of excellence, and outcome information that allows for the careful and appropriate application of these therapies.

Optimal Therapy for Rare Disorders and Genetic Diseases: Ethical and Political Challenges – Stuart MacLeod

Stuart MacLeod, Professor of Paediatrics at the University of British Columbia, opened his discussion stating that the term “orphan” may be applied to drugs, diseases or patients. He argued that the National Pharmaceutical Strategy (NPS) term Expensive Drugs for Rare Diseases (EDRD) is an example of imprecise terminology and serves as an obstacle. He went on to highlight the different provisions of orphan product policy in three jurisdictions: US, Australia and the EU.

Stuart discussed several key issues concerning drugs for rare diseases. Some of the more prominent concerns were outlined as follows: the interests of those who suffer from a rare disease may conflict with interests of policymakers and payers, logistical and geographic limitations on data accrual for rare diseases, extraordinary expense of clinical investigation, necessary reliance on surrogate markers, scientists with greatest level of expertise in rare disease likely to be engaged in studies, randomized controlled trials (RCTs) versus evaluation of real world safety and effectiveness, and health economic/outcomes review are not feasible at an early stage. When looking at the processes in Canada, Stuart stated that orphan products are flagged as an issue by federal/provincial/territorial ministers of health, and fall under the National Pharmaceutical Strategy.

Stuart posed the following discussion questions to participants: What is the extent of deviation between societal values and efficiency when deciding reimbursement and access? What is the impact of rarity on incremental cost per QALY? Regarding disease natural history and treatment outcomes (effectiveness): How is it possible to accommodate uncertainty attributable to limited data and difficulties in conducting RCTs with small numbers of patients? Bringing the social component into the health technology assessment and economic evaluations is attractive and probably unavoidable. How can it be made representative, valid, sensitive to resource allocation considerations, reflective of preferences (individual and societal)? Stuart reiterated that these questions are meant to help facilitate discussion throughout the day.

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

Stuart ended his presentation by highlighting the Orphan Drug Dilemma. From a utilitarian point of view it is unethical to invest substantial amounts of resources for a rare condition, as it is not maximizing society's benefits. From a moral perspective, society has an obligation not to abandon individuals who are affected by a serious but rare condition for which no treatment exists. Lesia Babiak agreed with Stuart but stated that there exists a huge sticker shock associated with orphan drugs for payers. Stuart commented that costs are high but also fair and explainable. For complex biologics there is a huge amount of investment that takes place. The cost of development is not zero and the price is linearly relative to diseases. Recouping some of the cost of development takes place only when that drug is on the market. With respect to payment, it is easier for private payers as they appear to have greater flexibility. National payers might want to do it but the “iceberg” fear is too large to overcome. Private payers have the room to increase the premiums; the public does not as they are trying to contain costs.

A Patient's Perspective on Access to Innovative Therapies for Rare Disorders – Ed Koning

Ed Koning, President of the Canadian Fabry Association, provided a brief overview of Fabry disease highlighting that it is one of only a few severe life-threatening Lysosomal Storage Disorders (LSD). Ed provided some statistical information surrounding the disorder, stating that it is classified as an ultra orphan disease (affecting 1 in 117,000) and life expectancy for male patients is between 40-50 years of age. Without enough of the enzyme, alpha galactosidase, the fatty GL-3 substance builds up in cells of the body causing amongst other things: strokes, heart attacks, kidney failure, extreme pain, inability to sweat and tolerate high temperature, gastrointestinal problems and inability to gain weight, hearing loss, and vertigo. Ed commented that he is now 48 years old and has serious health problems. He has already had a kidney transplant, and remains at high risk for a heart attack and has already suffered from several strokes, hearing loss and imbalance.

Enzyme Replacement Therapy (ERT) is the only effective treatment for Fabry disease. It is made using recombinant genetic technology and administered once every two weeks via intravenous. The treatment costs about \$250,000 per year per patient. It has been available in over 40 countries such as Croatia, Argentina, Brazil, Turkey, and Bulgaria for several years. ERT was approved for use in Canada in early 2004 by Health Canada but still not accessible to patients. In May 2001 Ed began an experimental ERT for the treatment of Fabry disease.

Ed highlighted that Canada remains the only developed country in the world that does not have an orphan product policy. The main challenges were and still are the high cost of treatment, the Health Ministers reliance on the inter-provincial Common Drug Review (CDR) and Canadian Expert Drug Advisory Committee (CEDAC), and the negative decisions from the CDR. In order to communicate the issue surrounding rare disorders Ed has networked with others to speak with a unified voice. He has become an expert on the issues of the disease as well as how the Canadian health care system works and how decisions are made. He has operated at arms length with biotechnology and pharmaceutical companies. He feels one of the most important aspects of his work is

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

educating the various decision makers. Despite the virtual unanimous recognition that CDR is not correct body to determine funding of life saving orphan drugs patients still have extremely limited or no access to ERT. Canadian criteria are among the most stringent in the world. Health Ministers now suggest the Fabry agreement be used as a model for Expensive Drugs for Rare Disorders (EDRD), as part of National Pharmaceutical Strategy (NPS). Ed stated this is completely unacceptable.

Ed championed the idea of collecting real world, post market data on orphan drugs via international patient registries and standards. He called for the elimination of unnecessary bureaucracy and research protocols that provide little scientific or clinical value. Ed highlighted that the small numbers of patients in Canada means that we should be studying those proven models already in place that are less cumbersome/expensive. He strongly believes that patients need to be involved in decision making processes. Canada requires an orphan product policy that effectively addresses access to orphan drugs and therapies (i.e. ERT for Fabry to be administered as a preventative therapy prior to organ failure).

Criteria and Values in Healthcare Priority Setting – Lydia Kapiriri

Lydia Kapiriri, Research Associate at University of Toronto Joint Centre for Bioethics, gave a presentation on priority setting within healthcare. She began by stating that priority setting is defined as the distribution of resources between competing programs and people. The relevance of priority setting within the health care spectrum is that there exist seemingly infinite health demands on a finite health care budget.

Lydia outlined several different phases of priority setting. In the first phase, there is a tendency to look for quick fixes and simple solutions (result is the current framework of cost effective analysis). In the second phase, there is a realization that quick solutions are flawed and practically difficult to implement. In the third phase, priority setting becomes a political process. Common values and criteria in priority setting for disease related/medical criteria include cost-effectiveness, maximization of benefits, treatment outcome/ benefit costs, efficiency, quality of evidence on effectiveness, severity/urgency, and number of people affected. The value dilemma centres on a lack of agreement about what values should guide priority setting. Lydia made a point of noting that the use of a cost effective analysis (CEA) is a value judgement. Some values are applied implicitly. Because it is value laden there is a need to involve legitimate stakeholders and a need to adopt ethical guidance to create fair processes.

Different countries have different values with respect to HTA. Direct public involvement in actual decision making is exemplified in the UK through the citizen's jury at NICE. This is an example of eliciting public values and directly incorporating them in priority setting. Looking forward we need to understand and document actual priority setting processes for orphan drugs. Do the current processes need to be adapted (to make them fairer) or is a different process necessary for orphan drugs? We need to know societal values for priority setting for orphan drugs in Canada. Lydia noted that it is equally important to determine whose values are important.

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

Lydia recommended a separate process for priority setting for orphan drugs that includes an ethical basis/moral obligation, distributive justice, and non-abandonment. Since CEA is valuable but inadequate, include other values like assigning equity weights in HTA for orphan drugs. Lydia commented that one could propose publicly elicited additional criteria for an orphan drug assessment. This would ensure stronger ‘public’ and other relevant stakeholders’ involvement and fairness in priority setting for research and development and HTA for orphan drugs.

HTA and Canadian Access to Drugs for Rare Disorders – Durhane Wong-Rieger

Durhane began her presentation by describing CDR’s mandate and highlighting the inappropriate application of HTA to rare disorders. Durhane noted that even the former chair of CEDAC acknowledged that the CDR was an inappropriate body to evaluate drugs for rare disorders. Often, the unique issues of rare disorders are not considered. When dealing with a small patient population, you will have less robust clinical trials data. For previously untreated disease there has to be recognition that we do not have current drug comparisons. Overall there is far less experience with rare disease and surrogate markers and a lack of long-term data outcomes or impact on survival are not always available. CDR/CEDAC re-reviews safety and effectiveness and do not use Health Canada assessments.

Durhane drove the message that HTA cannot work for rare disorders. CDR/CEDAC applies the same HTA for common drugs such as cost comparison, cost-effectiveness, cost-utility, and opportunity cost. Durhane pointed out that CDR/CEDAC recommends “not to list” almost every drug for rare disorders and then provincial drug plans conveniently defer to CDR/CEDAC recommendations. There is an incredible level of inconsistency across provinces in terms of access; with private drugs plans; and with the international patient community.

Durhane commented on the F/P/T proposed EDRD program which is meant to provide the national solution to drugs for rare disorders. This was produced in response to the potential geographic imbalance of some rare disorders, causing disproportionate impact on some provinces or creating incentives for patients to move. Durhane mentioned that the program is based on the “pilot” response to Fabry and MPS I “evidence-based” guidelines defining eligible patients. There is a research protocol to register patients and collect post-market data, which is time-limited to allow for review and decision to continue. This program is potentially harmonious with Health Canada’s Progressive Licensing Framework and may or may not require a CDR/CEDAC recommendation.

Genetic Disease – Denis Fiset

Denis provided a familial experience of dealing with genetic disorders. Denis lost his daughter to Tay-sachs disease when she was 2 years of age. He was surprised at how little is told to families who are faced with rare genetic disease. Largely, he sees this as a result of physicians knowing very little. Some segments of the population are very well protected through screening and testing mechanisms. However, there are no statistics on deaths from genetic/rare diseases in Canada. How can we prevent, treat or cure a disease we know virtually nothing about? One thing Denis discovered was that hospitals

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

and physicians are not talking to one another and he was shocked by the lack of harmonization. Is the government ready to apply solutions? Denis sees the key obstacles as cost and lack of expertise. If a recommendation is made, all provinces should follow suit. Should it not be mandatory?

Assessing the Economic Challenges posed by Orphan Drugs – Michael Drummond

Mike Drummond, of the University of York in London, presented the key conclusions elicited at the London Round Table on Orphan Drugs. He stated that the annual treatment cost for orphan drugs is related to patient population but that access to orphan products varies across Europe. Mike commented that ‘standard’ methods of HTA are inadequate for orphan drugs. Social value may deviate from cost-effectiveness in the case of orphan drugs and a large research agenda.

Mike recommended that the research agenda of HTA for orphan address the following: To what extent does societal value deviate from efficiency in the context of orphan drugs? How does rarity impact on the incremental cost per QALY? How could patient registries be used to accumulate knowledge on effectiveness and societal value of orphan drugs? How do current processes for assessing and appraising drugs need to be adopted? With respect to the funding development and use of orphan drugs, is the traditional way of funding research into drugs for rare diseases sustainable? At what level in the healthcare system should budgets for orphan drugs be set? How can funding schemes be developed to allow access to orphan drugs, yet provide assurances to payers that funds are not being wasted?

According to Mike the objectives of this meeting are twofold. First, we need to promote a dialogue amongst thought-leaders and stakeholders on HTA methods for orphan products. Second, thought-leaders should be assembled together to discuss and outline an HTA methods research agenda for orphan drugs.

Mike asked the group if there exists adequate information to undertake an HTA. How do orphan drugs look when judged against existing cost-effectiveness thresholds? Should additional societal considerations be introduced; if so how? There was a great deal of discussion surrounding the incorporation of societal values into HTA. Participants agreed that HTA is broader than cost-effectiveness. There is a need to study how different HTA agencies engage different stakeholders, and establish process to better incorporate societal values. What are the specific attributes of the social value function? How can the process be improved from the decision-making process? Mike highlighted the importance of determining where on the continuum a distinction is made. He also recommended that stakeholders explore geographical differences across jurisdictions. Consider an issue broader than orphan drugs and define a decision process to determine where societal values emerge. Mike suggested that participants look to offer a trial of life that will adhere to stopping rules and examine different approaches to conditional reimbursement.

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

According to Mike it is paramount to engage all stakeholders in the policy process. There is a need to determine whose values should count and how much. He advocated on behalf of the patients, stating full patient engagement is a fundamental component. Engagement must be meaningful and must give consideration to the caregiver. In order to generate better evidence on orphan drugs, individuals need to get prior agreement from key parties (e.g. patient reimbursement agencies) on design (including definition of a positive outcome) of clinical trials. Mike championed the use of adaptive trials designs, improved design and use of cohort studies (i.e. Registries), and international collaboration in studies of orphan drugs (pre- and post-launch). When it comes to funding innovation, which models should be employed? Has anyone come up with a way of doing this? Mike suggested that that it may be necessary to create the market. Perhaps the focus should be on studying the willingness-to-pay for innovation.

Commissioning for Rare Disease in England – Edmund Jessop

Edmund Jessop, medical adviser at the National Specialist Commissioning Advisory Group (NSCAG), outlined three components of commissioning for rare disease in the UK which include planning, funding, and monitoring. In the UK they do not have separate 'drug' budgets, instead they fund services. In addition, they commission services so there exists no category of "rare disease," the category is "specialised services." Edmund provided a brief overview of the National Health Service (NHS) in England. The NHS covers everything from acute care to long term health care, from primary care to drugs whether in hospital or at home. In England the population base is roughly 50m people and they have a global budget of almost £90 billion. The NHS budget is split into local budgets but hospitals do not get money directly from the Department of Health. All the NHS money (after some topslicing) goes to the primary care trusts to fund services for its members. Hospitals get their money from primary care trusts by treating patients of each primary care trust. The planning component is broken down as follows: local 100,000; Local collaborative 1,000,000; National 5m – 50m. Commissioning budgets are only held at two levels with almost all at primary care trusts (about £50bn) but there is a small budget for national NSCAG commissioning (about £250m). Primary care trusts collaborate to commission specialist services such as renal, cardiac and cancer. These collaborative arrangements are known as specialist commissioning groups. National commissioning is done by the NSCAG team. The main driver is clinical, to ensure patients are seen by well-practiced teams. However, most of the services covered are also very expensive, typically more than £50k per patient so the system acts as a financial risk pool. But expense alone is not the driver because a patient with severe haemophilia may cost more than £500k in Factor VIII replacement but haemophilia is not on the NSCAG list.

The monitoring component looks at outcomes, peer review, patient experience, and access geography. According to Edmund, clinical monitoring is important to NSCAG. This is easier for the surgical services, but difficulties persist in defining outcomes for many of the medical services. Due to the fact NSCAG centralises they also need to monitor the geography of access.

Edmund used lysosomal storage disorders to demonstrate how the medications are financed. With enzyme replacement therapies the risk pool needs to be large, national

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies**

in the UK case. Even a pool covering 5m people will show substantial variation. In England and Wales, health technology assessment is NICE or nothing. There is no separate system for ‘catastrophic’ or ‘life saving’ drugs.

Conclusions and Recommendations

Durhane asked participants to comment on of how we define Canadian values and offer suggestions on which values should take precedence. Should we not adopt a similar process in Canada to that which is applied in the UK where no one is left behind? Do Canadians not believe that everyone deserves an equal chance? There was agreement that we need to look at the severity of the disease and the lack of access, before looking at specialized services. It was also agreed that is it right, reasonable and necessary for all patients, including those with rare disorders, to access treatments. Many felt this should be a statutory law in Canada. The group is not seeking special consideration around evidence and data. They are looking for Canadian regulatory bodies to adopt international standards. As was demonstrated in the UK case, patients are agents of their own health; they will not take a drug that does not help them.

Stuart closed the meeting by asking the audience if the process in Canada for drug reimbursement is fatally flawed. Is a new vehicle needed? There was a resounding yes by all attendees. There absolutely has to be some recognition on behalf of agencies like CDR/CEDAC that these issues are different. This means we need to create an initiative. At this point, we are not creating much progress. Learn from the models already in use, identify a high profile champion, and modify our HTA approach. These patients are therapeutic orphans and the public needs to be made aware of the benefits of early intervention.

**Forum 3:
Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and
Therapies**

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Forum 3:

Canadian's with Rare Disorders – Assuring Access to “State of the Art” Diagnoses and Therapies

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