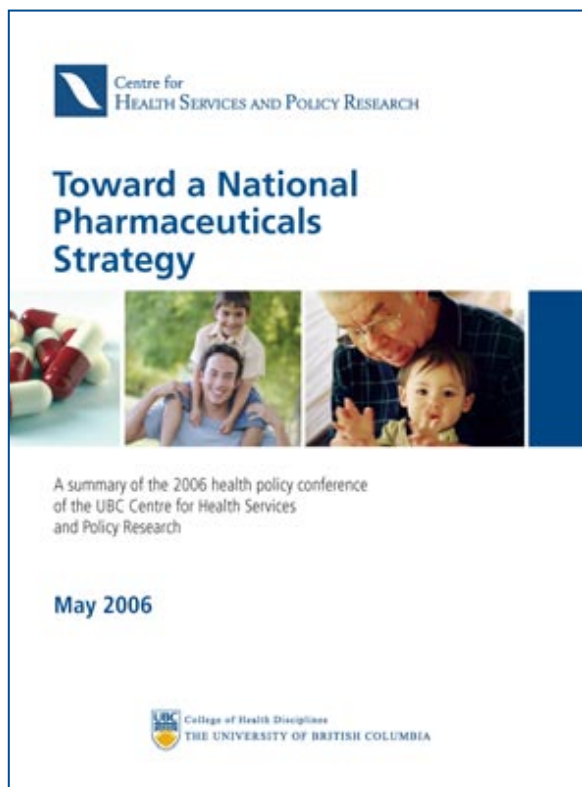


Toward a National Pharmaceuticals Strategy

A summary of the 2006 health policy conference
of the UBC Centre for Health Services
and Policy Research



May 2006

Toward a National Pharmaceuticals Strategy

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About CHSPR

The Centre for Health Services and Policy Research (CHSPR) is an independent research centre based at the University of British Columbia. CHSPR's mission is to stimulate scientific enquiry into issues of health in population groups, and ways in which health services can best be organized, funded and delivered. Our researchers carry out a diverse program of applied health services and population health research under this agenda.

CHSPR aims to contribute to the improvement of population health by ensuring our research is relevant to contemporary health policy concerns and by working closely with decision makers to actively translate research findings into policy options. Our researchers are active participants in many policy-making forums and provide advice and assistance to both government and non-government organizations in British Columbia (BC), Canada and abroad.

CHSPR receives core funding from the BC Ministry of Health to support research with a direct role in informing policy decision-making and evaluating health reform, and to enable the ongoing development of the BC Linked Health Database. Our researchers are also funded by competitive external grants from provincial, national and international funding agencies.

Much of CHSPR's research is made possible through the BC Linked Health Database, a valuable resource of data relating to the encounters of BC residents with various health care and other systems in the province. These data are used in an anonymized form for applied health services and population health research deemed to be in the public interest.

CHSPR has developed strict policies and procedures to protect the confidentiality and security of these data holdings and fully complies with all legislative acts governing the protection and use of sensitive information. CHSPR has over 30 years of experience in handling data from the BC Ministry of Health and other professional bodies, and acts as the access point for researchers wishing to use these data for research in the public interest.

About the Conference

Canada's federal and provincial governments have set out to improve and coordinate pharmaceutical policy initiatives through the development of a National Pharmaceuticals Strategy (NPS). The 2006 health policy conference of the UBC Centre for Health Services and Policy Research—Toward a National Pharmaceuticals Strategy—brought together national and international experts to discuss key issues facing the NPS.

Conference registration was open to all, and among those registered were 17 representatives of health professions, 20 representatives of community and patient advocacy groups, 50 representatives from the pharmaceutical, insurance and consulting industries, 86 decision makers and employees of public agencies in Canada, and 104 researchers from Canada, the United States, Australia, the United Kingdom and Mexico.

We are pleased to offer this summary of the ideas presented at the conference, and look forward to the continued evolution of these important initiatives.

Executive Summary

Policy Context

“Drug policy is an incredibly complicated mix of scientific evidence, judgment, altruism, self-interest and politics, and it’s all superimposed on a complex, semi-rational, constantly changing, over-burdened health care system.”

— Dr Andreas Laupacis (Canada)

Costing nearly \$20 billion, prescription drugs are the second-largest and fastest-growing component of health care spending in Canada. While many drugs offer significant value to particular patients, every dollar of pharmaceutical spending is, by necessity, a dollar diverted from other health, social and educational programs. Policy must therefore strive to make the best possible use of resources to improve the health and wellbeing of Canadians.

Nearly two out of every three Canadians will fill at least one prescription this year. Some medicines are over-used, others under-used, and many are misused. Optimal use is a function of how pharmaceuticals are evaluated, priced, marketed, prescribed and financed.

There is no single ‘magic bullet’ in the realm of pharmaceutical policy. Rather, an integrated approach to coordinating a host of interrelated policies—like the approach articulated by Canada’s NPS—will be critical to ensuring that desired outcomes are obtained in a safe, equitable and sustainable fashion.

Drug Coverage Policy

“The issue of transparency is very important. That involves not only pharmaceutical companies and device manufacturers. It also involves professionals ... patient groups ... and [assessment and funding] organizations like the ones represented here.”

— Sir Michael Rawlins (United Kingdom)

Resources are limited. Tough choices must be made about which drugs will be funded and which will not. Cover-

age decision-making should incorporate the best available scientific evidence, as well as public values and priorities. It should consider the broad health, economic and societal implications of coverage decisions.

The Common Drug Review (CDR) has begun to standardize and improve Canadian processes for making drug coverage decisions, but faces challenges similar to those faced by agencies in other countries. These include the licensing of drugs based on selective clinical trials data of uncertain value in terms of actual health outcomes, and the suppression of scientific data by drug manufacturers.

Canada should work with other countries to address common challenges. Together, for example, national governments could mandate public registration of all clinical trials and full disclosure of all data used in coverage decision-making. Information, ideas and processes can, and should, be shared.

Managing Drug Prices and Expenditures

“The pharmaceutical industry doesn’t particularly like to compete on price but it will if the environment is set in such a way that it’s encouraged to.”

— Mr Wayne McNee (New Zealand)

When based on sound principles and scientific evidence, national formularies, reference pricing and purchase tendering effectively manage drug expenditures, while also ensuring access to medicines.

New Zealand’s unique success in this area suggests that the most powerful cost management instrument available to governments is a fixed budget. A budget explicitly defines what society believes is an acceptable amount to spend on medicines—taking into consideration private uses of resources and public uses of health and social services. This encourages price competition within older drug classes, and can generate the savings necessary to fund cost-effective breakthrough medicines.

The lack of universal drug coverage hinders expenditure management in Canada. It fragments negotiating power and prohibits a deliberate process of defining a drug budget. Until pharmacare in Canada becomes more comprehensive, expenditure management must be coordinated across multiple levels of government and both the private and public sectors.

Improving Quality Use of Medicines

“One of the biggest challenges ... is not so much drug subsidy—it’s how we deal with behavioural change in stakeholders with respect to achieving the outcomes we know these drugs can get.”

— Dr Lloyd Sansom (Australia)

Once the potential benefits of a medicine are proven and a product is covered by public plans, policy must shift to focus on generating the information and behaviour necessary to achieve the desired outcomes and to avoid the perils of misuse, over-use and under-use.

Promoting the quality use of medicine requires comprehensive policy approaches to improving information and engaging health professions and the public. This would include drug utilization monitoring and review, evidence-based electronic prescribing systems, guideline development, ongoing educational initiatives for the public and health professions, and more.

To ensure the maximum impact and longevity of quality use initiatives, the public and health professions must be involved in the process from the start. Moreover, given documented bias and the use of non-scientific persuasion in pharmaceutical industry marketing activities, investments in this policy domain must be public investments—made by those accountable to Canadian citizens.

Monitoring Drug Safety

“We have to stop thinking of the regulatory process as a black box and think of it as a continuous stream. Once products are on the market, we still need to look for evidence of safety.”

— Dr Mary Wiktorowitz (Canada)

Though critical in establishing the safety and efficacy of medicines, randomized controlled trials used to obtain market licenses have well recognized limitations—they study small populations for short durations and focus on limited outcomes. Once on the market, determining the ‘real world’ safety of a drug requires complementary monitoring and evaluation approaches—a systematic approach to post-market surveillance.

Many countries (including Britain, France and the United States) have already initiated various elements of post-market surveillance. Emerging plans in Canada would implement active adverse reaction reporting, ongoing drug utilization review, and real-world clinical trials overseen by a network of research centres and government bodies.

Timeliness in assessments, reviews and the dissemination of research findings is crucial for effective safety monitoring and related policy development. Much of the material currently being produced does not arrive in time to inform decisions. Canadian investments should be designed to build capacity for timely surveillance and to connect the research and policy communities at the local and national levels.

NPS Process and Public Ownership

“The National Pharmaceuticals Strategy is a major initiative driven by the first ministers of this country to deal—together—with difficult issues.”

— Dr Penny Ballem (Canada)

Historically uncoordinated pharmaceutical policy in Canada reflects the division of jurisdiction between federal and provincial governments. By establishing the NPS, Canada’s First Ministers have recognized that leadership is required to overcome jurisdictional challenges, and that a significant investment is necessary to bring about sound policy in this important area of health care.

Common sense and international experience indicate that transparency and public participation are essential to the success of NPS policy initiatives. Pharmaceutical policy is public policy. While the insights and expertise of specific stakeholders—manufacturers, professionals, researchers and patient groups—are an important input into decision-making, the processes, evidence and rationale behind policy should be transparent and accountable to broader society.

Canada’s NPS is a bold and important policy initiative. While there is no ‘magic bullet,’ many of the systems required for integrated pharmaceutical policy are already in place. By investing in these systems and through increased coordination, transparency and public involvement, the NPS has the potential to significantly enhance safety, effectiveness, equity and efficiency in Canada’s pharmaceutical sector.

Conference Session Summaries

Context and Challenges

Penny Ballem *Deputy Minister, Ministry of Health, British Columbia, Canada*

Penny Ballem opened the conference with a brief introduction to the challenges facing British Columbia's health care system in general, and its public drug plan in particular.



Penny Ballem, Ministry of Health, BC

“The health care system has enormous scope, and the complexities of the issues across it are significant,” Dr Ballem said. Beginning with health promotion and prevention, the system moves through health protection, primary care, community programs and acute care, and then through a spectrum of independent living, assisted living and residential care. New demands and expectations arise continually across the continuum: new vaccines, new initiatives, new technologies, and new issues and challenges. Governments’ challenge is to provide a balance of services across that continuum that will offer the best results.

Sustainability is a major challenge facing all public drug plans, acknowledged Dr Ballem. In British Columbia, assuming an economy with annual growth in revenues of three per cent, annual growth in education spending of three per cent and annual growth in health spending of eight per cent, health spending will account for 71 per cent of the province’s budget by 2018 (Figure 1). As a result, the underlying social, economic, environmental and behavioral factors that contribute to population health will no longer be a primary focus for government, because it will be spending all its resources delivering health services, education and public protection—clearly not a sustainable picture, noted Dr Ballem.

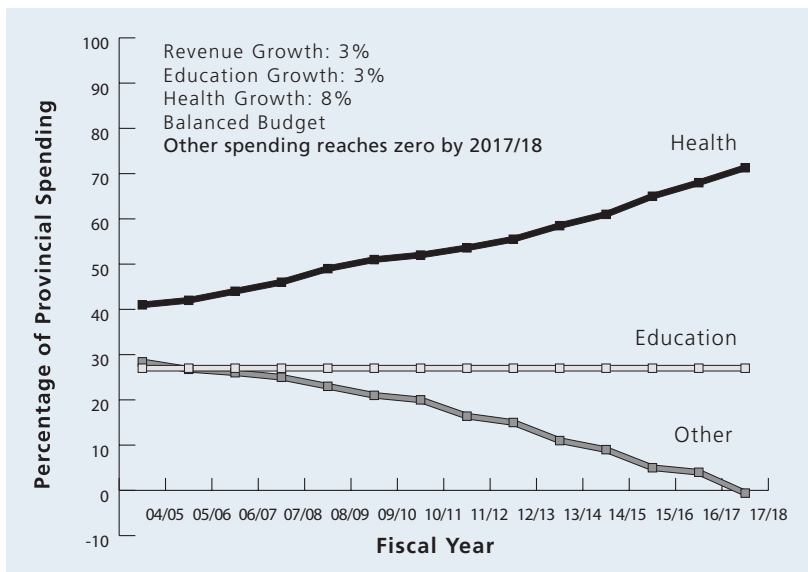


Figure 1
Revenue/Spending Scenario
Reproduced from presentation slides, Toward a National Pharmaceuticals Strategy, 2006.

Within this already demanding environment, the administration of a public drug plan presents even more challenges. In any Western government, argued Dr Ballem, the most difficult file to manage is the public drug plan file. “Some of the most significant advances in health care have been made in this area, but the sustainability of providing access to important pharmaceuticals is a huge challenge for governments around the world. In addition, it is an area with an extremely diverse range of stakeholders, all with very legitimate concerns.”

While British Columbia’s population increased by approximately ten per cent between 1995 and 2005, the number of paid prescriptions per beneficiary of the province’s main public drug plan increased by about 45 per cent. As a result, spending increased by 110 per cent over the decade—and clearly population growth and demographic change are not the primary factors driving that growth. At the same time, it is important to note that public drug plan spending in British Columbia is increasing at nine per cent a year, significantly below Canada’s national average of 13 to 14 per cent.

So governments, health care providers and the public face tough decisions. How do we balance competing priorities? How do we provide affordable access to important classes of drugs and new breakthrough drugs? In short, Dr Ballem asks: What are the decisions we have to make in order to maintain a public drug plan and ensure that everyone has access to the pharmaceuticals they need?

Dr Ballem also addressed the issue of breakthrough drugs, noting that very few newly released drugs in Canada meet

Patented Medicine Prices Review Board criteria to be classified as breakthroughs. The vast majority are line extensions or what are often called *me-too* drugs. The challenge lies in judging those incremental advances and comparing their value to advances in other areas of the system—new addictions programs, new vaccines, new hip replacement techniques.

The National Pharmaceuticals Strategy (NPS) is an initiative driven by Canada’s first ministers in an effort to deal with some of these difficult issues. Key focuses of the NPS include catastrophic drug coverage, expensive drugs for rare diseases, drug pricing and purchasing, and real-world drug safety and effectiveness. Dr Ballem noted that British Columbia has launched complimentary initiatives in many of these areas, and that opportunities for cooperation certainly exist, particularly around financing expensive drugs for rare conditions and the complex issues surrounding a common national formulary.

Dr Ballem highlighted British Columbia’s e-Therapeutics initiative, which is investigating how new information technologies can be used to support quality use of medicines. Electronic prescribing, part of the province’s electronic health record agenda, is being aggressively pursued.

The province also leads the country in its approach to chronic disease management through collaboratives said Dr Ballem. The Congestive Heart Failure Collaborative, launched in 2003 across a population of 100 physicians and 1,000 patients, has greatly increased the percentage of patients receiving appropriate baseline standard medications for congestive heart failure.

Evidence, Economics and Values in Coverage Decisions

Tony Culyer *Chief Scientist, Institute for Work and Health, Canada*

Pharmaceutical policy often involves complex decisions—and processes that are evidence-informed, deliberative, and well suited to making complex decisions are relatively rare in social policy, and new to health care.

Tony Culyer opened the session by defining evidence as anything that is *a relevant empirical fact or that gives a reason for believing a fact*. He identified three types of evidence: colloquial, scientific and context-free, and scientific and context-sensitive.



Tony Culyer, Institute for Work and Health

Colloquial evidence is unsystematic and idiosyncratic. It combines multiple sources, at least one of which may be personal or professional experience. So cost-utility algorithms may be presented together with political acceptability, or public attitude data may be combined with vivid recollections or personal encounters—“unscientific assertions articulated by people imbued with the aura of science.”

American expert opinion in the 1930s regarding prone sleeping is a prime example of the disadvantages of colloquial evidence. Experts, including Dr Benjamin Spock, recommended that infants be placed on their stomachs while sleeping, in large part to reduce the risk of choking or aspiration pneumonia if vomiting occurred. We now

know that this apparently rational, theory-based, authoritative and well-intentioned advice has led to tens of thousands of avoidable sudden infant deaths. But we also can't be too dismissive about colloquial evidence, warned Dr Culyer, particularly in the absence of scientific evidence.

Scientific evidence is distinctive in its analytical approach. While the things about which evidence is gathered may be apparently unscientific, like people's health, cognitive development or values, the evidence itself can be created or gathered, and analyzed or interpreted, scientifically.

Dr Culyer and Dr Jonathan Lomas have identified two types of scientific evidence: context-free and context-sensitive. Context-free evidence enjoys maximum generality but always needs to be interpreted in a particular context of application, such as efficacy or effectiveness—for example, the results of randomized control trials or meta-analysis of trials. Context-sensitive evidence, on the other hand, is prepared, interpreted and presented for maximum applicability in a particular context—for example, cost-effectiveness in British Columbia's primary health care sector in a particular year.

Deliberative processes gather information from a wide variety of sources—often including external groups, stakeholders and the public. They both elicit and combine evidence. Public and expert knowledge, and colloquial and scientific evidence, are taken into account through deliberative processes. This sets them apart from consultative processes, which often gather information through social surveys, public meetings and witnesses. Deliberative processes are perceived to increase the likelihood of achieving sound, reasonable and acceptable decisions, and are commonly seen as desirable when the issues at stake are contentious.

How do we define difficult decisions? Dr Culyer identified at least seven characteristics: a high ratio of colloquial evidence to scientific evidence; sparse, inconclusive or hotly contested scientific evidence; significant professional opposition; issues are raised that aren't covered by standard guidelines; ineffective technology that faces political or public pressure for adoption; effective technology that faces political or public pressure for rejection; or a decision is needed quickly.

Based on these characteristics, it is clear that most decisions in the social policy context are difficult, primarily

because of the relative lack of scientific evidence and the preponderance of colloquial evidence. Health care, particularly pharmaceutical care, is different, however. It enjoys a relatively recent tradition of generating scientific evidence, both context-free and context-sensitive, in which colloquial evidence plays an integral role rather than serving as a substitute for research-based knowledge. In this regard, Dr Culyer suggested: “Health care might become exemplary, kind of a beacon for decision-makers and researchers in other fields of social policy to follow.”

Sir Michael Rawlins *Chair, National Institute for Health and Clinical Excellence, United Kingdom*

Sir Michael Rawlins chairs the National Institute for Health and Clinical Excellence (NICE), which provides national guidance on the promotion of good health and on the prevention and treatment of illness in the United Kingdom. He detailed the Institute’s use of evidence in assessing health technologies and developing clinical guidelines.

NICE has available to it evidence from a variety of sources: randomized control trials, non-randomized control trials, systematic reviews and meta-analyses of trials, before-and-after studies, case-control studies, and opinion. While traditional approaches have placed these forms of evidence in hierarchies, Sir Michael believes that this approach has major faults, not the least of which is that it tends to elevate technologies that have been subjected to randomized control trials, often magnifying small effect sizes against other issues.

“If we relied on randomized control trials and gave them such an important role, we would find ourselves still using thalidomide, we would not accept any association between smoking and lung cancer, and we would not defibrillate patients when they go into ventricular fibrillation,” he noted. So instead of using hierarchies, NICE looks for evidence that is fit-for-purpose.

In terms of economic evaluation, NICE uses two broad approaches: cost-minimization and cost-effectiveness. In cost minimization, if two technologies do the same thing, the less expensive one is recommended. However, demonstrating equivalence is difficult. More often, the Institute attempts to determine whether the health gains claimed by a particular technology warrant the increased cost.

However, determining cost-effectiveness is also a challenge. NICE has adopted a flexible, case-by-case approach, which takes into account a number of important features: the degree of uncertainty surrounding cost-effectiveness estimates; any special features of the condition being treated; reference to previous appraisals; consistency; the innovative nature of the technology; and wider societal interests.

Typically, technologies that cost between £5,000 and £15,000 (UK) per quality-adjusted life year (QALY) added are unlikely to be rejected on the grounds of cost-effectiveness. Those costing £20,000 to £30,000 must supply increasingly compelling rationales in order to be accepted. To date, no technology costing more than £50,000 per QALY added has been accepted by NICE.



Sir Michael Rawlins, NICE

Sir Michael concluded his session by discussing values and process. In determining whether to go above the threshold of £20,000 and £30,000, NICE often works with the Citizen’s Council, a group of 30 ordinary citizens, to decide what factors (such as age, gender, race, number of dependents, employment status and social status) should be taken into account when evaluating how health technologies should be used. Interestingly enough, the Council has advised against taking age, gender, race, familial status or social status into account.

While the process does have its challenges (for example, how to deal with the rule of rescue) it does help ensure that NICE’s decisions broadly reflect the opinions and values of the people it serves.

National Drug Assessment

Andreas Laupacis *Chair, Canadian Expert Drug Advisory Committee, Canada*

Canada's two-year-old Common Drug Review (CDR) is a single process for reviewing new outpatient drugs and providing participating publicly funded drug benefit plans with formulary listing recommendations. The CDR conducts a systematic review of the effectiveness of each new drug, which includes a critical review of a cost-effectiveness submission from the drug company. The Canadian Expert Drug Advisory Committee (CEDAC) forms part of the CDR process, and is an independent advisory body comprised of individuals with expertise in drug therapy and drug evaluation.



Andreas Laupacis, CEDAC

Andreas Laupacis, Chair of the Committee, noted several structural challenges to achieving standardized drug assessment across the nation. Canadian jurisdictions often have very different listing policies for particular drugs. For example, some provinces cover COX-2 inhibitors, while other provinces restrict coverage. Terminology also varies. A 'no' listing in some provinces indicates a drug won't be covered under any circumstances, while in others, a 'no' listing allows for exceptions. Dr Laupacis also noted the conflict between the desirability of consistent formulary listings across the country, and the necessity under the CDR to respect provincial control over health budgets. So despite the existence of the Review, Canada is a long way from standardizing formulary decisions.

These jurisdictional challenges are complicated by difficulties in getting and interpreting evidence. Is an accurate record of all the studies conducted available? Are all the results of a particular trial available, and if not, why not? "So I think we've got a long way to go," Dr Laupacis said. "There is a lot of talk about transparency around processes like the CDR, but I think there is also a great need for transparency in regard to getting information about drugs from clinical trials."

Dr Laupacis also noted the CDR is seeing more and more drugs that have been approved on the basis of surrogate markers. "For many of these drugs, we just don't know how the surrogate markers translate into clinical outcomes, and therefore it's virtually impossible to assess what the cost-effectiveness ratio for these drugs is."

Interpreting selected quality-of-life measures and functional status measures—for example, interpreting the changes seen with dementia drugs—is extremely difficult. Additional challenges include the lack of head-to-head trials, the short-term nature of clinical trials, and highly selective trial populations—all of which make it difficult to extrapolate results into the real world. And although post-market studies, particularly those designed to assess safety and classify utilization, are useful, Dr Laupacis cautioned that observational studies are less useful in assessing effectiveness.

The key to generalizing and incorporating information from clinical studies and making sound recommendations is increased transparency—on the part of both reimbursement committees and industry. Dr Laupacis would like to see committees include members of the public and patients, plain-language versions of recommendations, and open dialogue with the public, patient groups and professional societies. On the part of industry, full release of all information from clinical trials would be a major step forward. But transparency is also needed regarding the relationships between industry and guideline developers, and between industry and patient groups.

"Drug policy is an incredibly complicated mix of scientific evidence, judgment, altruism, self-interest and politics, and it's all superimposed on a complex, semi-rational, constantly changing, over-burdened health care system," said Dr Laupacis. Increasing openness and inclusiveness is a necessary part of legitimate priority setting. It won't make the decisions easy, but it will make them more transparent. "And hopefully the public will understand that these are incredibly difficult decisions—but they have to be made."

Wayne McNee *Chief Executive, Pharmaceutical Management Agency of New Zealand*

New Zealand's Pharmaceutical Management Agency (PHARMAC) is a standalone Crown agency reporting directly to the ministry of health. PHARMAC's staff of 45 is mandated to secure the best health outcomes possible for the population of the island nation.

In 2005, the Agency funded 27 million prescriptions. New Zealanders pay a modest fee for a three-month prescription, and once they reach 20 prescriptions, pay nothing more. They can also purchase non-funded drugs on the private market. PHARMAC Chief Executive Mr Wayne McNee noted that while the Agency has been successful in controlling expenditures, it has done so within a legislated, fixed budget, and in a nation without a strong industry presence.

PHARMAC's assessment process begins by gathering information, much of which is provided by the pharmaceutical industry. Any clinical component of the assessment is provided by medical, pharmacology and therapeutics committees.

When assessing a new drug, PHARMAC takes into account a wide range of criteria, including: cost-effectiveness; the health needs of the population (in particular, Maori and Pacific peoples); the availability and suitability of existing therapies; clinical benefits and risks; overall impact on both the pharmaceutical and health budgets; direct cost to health service users; and government objectives and priorities for health funding.

Potential savings elsewhere in the public sector are also analyzed, such as reductions in hospitalizations or nursing home costs. Extension of life and improvements in quality of life are also considered.

If the drug provides a cost saving to the health sector, it is funded quickly. If it represents an increased cost, and funding is available within the budget, PHARMAC prioritizes it against other new drugs being assessed. If it represents an increased cost and funds are not available, it is wait-listed until funds do become available. PHARMAC also negotiates with pharmaceutical companies, which can sometimes result in a drug becoming more cost-effective.

Finally, PHARMAC makes a decision. If the Agency decides not to fund a product, the supplier has the opportunity to approach PHARMAC again and provide further information. The Agency also consults widely with the health sector, including consumer groups, medical and pharmacy groups, and the pharmaceutical industry, on every decision made, by writing to each of the groups and posting letters online. Drugs that PHARMAC has funded range from those that represent substantial cost savings, to those costing up to \$140,000 (NZ) per quality-adjusted life year added.

Mr McNee provided an example of one of PHARMAC's more controversial decisions: declining to fund COX-2 inhibitors. Applications were received from pharmaceutical suppliers in 2000 and reviewed in 2001. A quick cost utility



Wayne McNee, PHARMAC

analysis indicated that the drugs offered relatively poor value, and had a substantial budget impact—over \$30 million (NZ) per year. A detailed analysis confirmed this, and indicated a cost of \$450,000 per quality-adjusted life year in high-risk patients. In 2003, despite being the target of intense lobbying, PHARMAC decided not to fund COX-2 inhibitors.

Mr McNee concluded his talk by identifying a number of the challenges that PHARMAC faces: accurate forecasting using estimated costs and future budgets; the subjectivity of decision-making criteria; funding high-cost drugs, and the social acceptability of not funding them; transparency versus commercial confidentiality; and lack of consistency in the quality of information submitted by industry.

Lloyd Sansom *Chair, Pharmaceutical Benefits Advisory Committee, Australia*

In 2005, Australia's Pharmaceutical Benefits System (PBS) subsidized 650 drugs at a cost of almost \$6 billion (AU), \$5 billion of which came from public funds. Pharmaceutical expenditures account for 16 per cent of Australia's public expenditure on health.

Under the National Health Act, Australia's health care system is required to provide timely, reliable and affordable access to necessary and cost-effective prescription medicines. Cost-effectiveness is enshrined in legislation—a drug can't be listed by the PBS unless it is deemed to be cost-effective by the Pharmaceutical Benefit Advisory Committee (PBAC), a statutory committee which advises the minister of health. PBAC consists of 18 clinicians, pharmacists, health economists and consumers.

Dr Lloyd Sansom, Chair of the Committee, described the process used by PBAC when assessing a new drug. The supplier, or sponsor, prepares a submission in accordance with a published set of guidelines. The submission is evaluated by one of four independent assessment groups, and PBAC must make a decision within 17 weeks of receiving the submission.

Sponsors can respond at every stage of the process: they can respond to the committee's comments, and are allowed to make brief presentations to PBAC. Sponsors can also resubmit a proposal an unlimited number of times, and under certain circumstances can seek an independent review of the committee's decision.

One of the key pieces of information that drug companies are required to submit to PBAC is a comparative evaluation—a summary of how the new drug compares with the drug or therapy it is intended to replace. This raises several issues around the choice of comparator and the amount of data provided. Sponsors are also required to estimate the extent of use of the new product, and the extent to which it may replace other drugs or therapies.

New drugs may be listed if it can be shown that they cost-effectively treat or prevent significant medical conditions that are not treated, or inadequately treated, by existing drugs. In some cases, a drug is given conditional approval, but unless patients experience a significant, cost-effective benefit, the drug is withdrawn. PBAC has used this approach with some major drugs, such as tumor necrosis factor alpha inhibitors (an arthritis treatment) and efalizumab (a psoriasis treatment).

These are difficult decisions, admitted Dr Sansom. "All I know is that we can't change the direction of the wind, but we can adjust ourselves to ensure that we go in the direction that we want. And that is to ensure that people get the drugs they want at a price that they as individuals and the community as a whole can afford."



Lloyd Sansom, Pharmaceutical Benefits Advisory Committee

Common Challenges, Opportunities for Cooperation

Sir Michael Rawlins *Chair, National Institute for Health and Clinical Excellence, United Kingdom*

Wayne McNee *Chief Executive, Pharmaceutical Management Agency of New Zealand*

Lloyd Sansom *Chair, Pharmaceutical Benefits Advisory Committee, Australia*

Andreas Laupacis *Chair, Canadian Expert Drug Advisory Committee, Canada*

Sir Michael Rawlins opened his second talk of the conference by pointing out some of the commonalities shared by Canada, the UK, Australia and New Zealand. All four countries have health care systems based on the principle of social solidarity: a civic responsibility to look after each other in times of need. The countries also share long-standing tensions between the principles of utilitarianism and egalitarianism—providing the greatest good for the greatest number on the one hand, and fairness and equal opportunity for all on the other. And all of these tensions compete at a time of budget and resource constraints.

So there are areas in which the four countries and their institutions are well suited to provide mutual support. “We need to be much more aggressive collectively, not individually, about having both the protocols and the results of clinical trials made fully available to us—and in a way that we can quote to those who read our advice and our guidance,” argued Sir Michael.

The issue of surrogate markers also needs to be pursued vigorously and collectively. Drug funding bodies—who ultimately have to try to translate surrogate markers into measures of improved quality of life or longevity—need to be included in discussions between industry and drug regulatory authorities. Similarly, the international community should be working towards standardization of surrogate markers.

Transparency is vital, regarding not only industry but also professionals and patient groups. “We need to be assured, and the public needs to be assured, that the decisions we make have not in some way been inappropriately conditioned by the interests of both professionals and of patient groups,” Sir Michael said.

Wayne McNee also identified opportunities for international and cross-sector collaboration. These include sharing assessments and other information with health professionals through secure websites, as well as the possibility of launching an annual international conference of the organizations responsible for funding recommendations and decisions.

Lloyd Sansom called for an international exchange of information and ideas on issues such as innovation bonuses and price indexing of comparators. International debate is also needed on the difficult issue of measuring patient outcomes in oncology—should agencies measure progression-free disease, progression-free survival, stable disease, or partial response? In terms of clinical trial design, he said, we have to recognize that the results from trials powered for initial registration are not necessarily suitable to help determine whether a drug should be covered under public plans.

In his talk, Andreas Laupacis also offered suggestions for collaborative action. They include mandatory registration of clinical trials, trial protocols and outcome measures, and increased use of head-to-head trials. Dr Laupacis echoed calls for the systematic review and international standardization of surrogate markers and quality of life measures to determine which ones are important and how they can be best extrapolated to clinical outcomes.

National Formularies and Generic Pricing

Wayne McNee *Chief Executive, Pharmaceutical Management Agency of New Zealand*

Pharmaceutical expenditures in New Zealand have increased by about three per cent a year since the Pharmaceutical Management Agency (PHARMAC) was established in 1993. Without the Agency, estimates indicate that New Zealand's drug expenditure in 2005 would have been \$894 (NZ) million higher than current levels (Figure 2).

1998, PHARMAC reached an agreement with Parke-Davis involving the listing of Lipitor, which included a 60 per cent reduction in the price of its ACE inhibitor, Quinapril. When reference pricing was re-applied to the entire ACE inhibitor group to reflect the lower price of Quinapril, only Roche responded, dropping the price of its ACE inhibitor, Cilazapril. This left 97 per cent of New Zealand's ACE inhibitor market incompletely funded.

In response, PHARMAC introduced an exemption for patients with chronic heart failure, allowing them to continue using their current ACE inhibitor, and subsidized patient

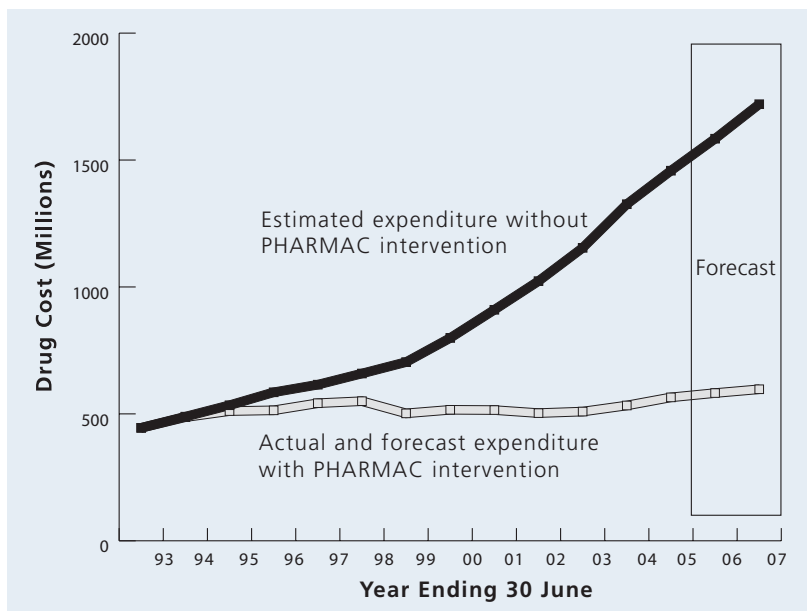


Figure 2

Impact of PHARMAC on Drug Expenditure Over Time

Reproduced from presentation slides, Toward a National Pharmaceuticals Strategy, 2006.

PHARMAC Chief Executive Mr Wayne McNee noted several keys to the Agency's success in managing expenditures in an earlier session, including fixed budgets, rapid assessments, and the lack of a strong industry presence in New Zealand. But PHARMAC uses a number of additional tools to manage pharmaceutical expenditure.

The first of these tools is reference pricing, which introduces similar prices for similar drugs. It is an economically efficient measure, argued Mr McNee: "Why would you pay more for things that are the same?" However, it can also be controversial. PHARMAC has evolved its reference pricing policies significantly over time, primarily by introducing exemptions for particular drugs under particular circumstances.

For example, when reference pricing was first applied to angiotensin converting enzyme (ACE) inhibitors in 1995, manufacturers reduced their prices in response—resulting in standardized pricing across the drug group. However in

visits to their physician to review their medication mix. PHARMAC also introduced a program informing physicians, pharmacists and patients about the changes. Finally, the Agency funded two evaluations of the exemption, both of which concluded that there had been a modest improvement in blood pressure levels in the 100,000 people who did end up changing from one ACE inhibitor to another.

Another important tool used by PHARMAC is the tendering of generics. There are several different types of tenders, but the most common involves multiple products. Tendering has resulted in significant savings in the generic market, allowing PHARMAC to shift resources to newer, more expensive drugs. Mr McNee noted that tendering also offers suppliers some benefits—markets are guaranteed for specific periods of time, and advertising costs are greatly minimized.

Requests for proposals are another useful expenditure management tool, and provide more flexibility than tendering.

In 2005, PHARMAC published a request for proposal for a recombinant factor VIII product—the resulting negotiation allowed the Agency to offer a range of product choices to patients and clinicians, and save about \$35 million over three years. Requests for proposals are also useful when more than one supplier is needed for a particular product—for example, influenza vaccine.

Package agreements bundle a range of products into a single agreement. For example, PHARMAC found that Gleevec was an effective, but expensive, treatment in all stages of chronic myelogenous leukemia. Negotiating with Novartis (the manufacturer) to reduce the price of 11 of its other products in a package agreement enabled PHARMAC to fund Gleevec in a way that was cost-effective overall.

PHARMAC negotiates contracts for most of the drugs that it lists, requiring manufacturers to supply the product on an ongoing basis or face financial consequences. This type of agreement is vital to New Zealand (a small country far from the source of supply) and offers suppliers protection from tendering and reference pricing. Some contracts include hard caps, which require suppliers to rebate any expenditure that exceeds pre-agreed-upon levels over the course of the contract. Soft caps are similar, but involve a risk-sharing arrangement—if sales exceed a pre-agreed-upon level, the supplier rebates a portion of the extra expenditure.

The Agency is the target of intense lobbying by individuals, medical groups and consumer groups. This takes the form of television ads, billboards, and newspaper ads advocating particular products. Mr McNee spends a great deal of time explaining how and why decisions were made to consumer groups, and PHARMAC increasingly includes consumers in its decision-making process through both an advisory committee and consumer representation on medical committees.

Any agency operating in this sort of heated environment needs the full understanding and support of government, noted Mr McNee. “When you put in place a system, you need to have a good understanding of the system in your government and among your ministers so they will understand the implications of it.”

This support will become even more vital to the success of PHARMAC—Mr McNee noted that the Agency has recently been charged with the challenge of funding oncology medicines, and has also started purchasing pharmaceutical-related products on behalf of hospitals in New Zealand.

Wayne Critchley *Former Executive Director,
Patented Medicine Prices Review Board, Canada*

The history of pharmaceutical price management in Canada reflects the division of powers in Canada’s constitution. Prior to 1987, the Canadian government tried to intervene in pharmaceutical pricing indirectly through the use of federal authority over patents. “So we had a long history of compulsory licensing to promote generic competition followed, when compulsory licensing came to an end, by the introduction of price controls through the Patented Medicine Prices Review Board,” noted Wayne Critchley.



Wayne Critchley, Former Executive Director, PMPRB

The PMPRB is mandated to protect consumers by ensuring that the manufacturers of patented drugs do not charge excessive prices. It was established in 1987 to embody the consumer protection pillar of the five pillars of federal pharmaceutical policy (the others are intellectual property protection, pharmaceutical research and development, international trade policies, and health care).

The Board is separate from public drug programs and reimbursement policies, and operates at arm’s length from government. Its mandate is limited to patented drugs and applies to all markets, including public plans, private insurance and cash-paying individuals.

Mr Critchley notes that the Board’s operations are relatively transparent: hearings are conducted in public, and its guidelines, policies and price reviews are published.

PMPRB regularly consults with key stakeholders, including provincial drug plans and ministries of health, and industry and consumer groups.

The Board's price guidelines are based on two key concepts: international reference pricing and therapeutic reference pricing. International reference pricing is designed to ensure that the Canadian price for a new, innovative drug does not exceed the international median (based on prices in the United States and six European countries). Therapeutic reference pricing is designed to ensure that the price of a new drug does not exceed the most expensive in its therapeutic class. In addition, price increases are limited to increases in the Consumer Price Index.

As a result of these policies, as well as the influence of provincial policies to manage drug prices, patented drug prices in Canada have been stable for the past 15 years, increasing at a rate below the Consumer Price Index and in line with trends in Europe. Canada used to have the second-highest drug prices in the world, with prices in 1987 23 per cent above the international median. Over the past decade, Canada's prices have consistently been five to ten per cent below the international median.

However, Mr Critchley noted that Canada's record on research and development is mixed. In 1987, with the end of compulsory licensing, industry agreed to double its research and development spending to ten per cent of sales. During the 1990s, they met and exceeded that commitment—however, in recent years the trend has changed, and internationally Canada now compares poorly with the other countries used in price comparisons.

There is also growing evidence that the prices of non-patented drugs—brand name, single-source drugs, multiple-source drugs, and generic drugs—are as much as 28 per cent higher in Canada than in other countries. As a result, in 2005, the first ministers expanded the mandate of the Patented Medicine Prices Review Board to monitor and report on the prices of non-patented drugs. Expanding the Board's authority to non-patented drugs makes sense for two reasons, argues Mr Critchley. It would produce a level playing field for all prescription drugs (not just patented drugs) and remove the prospect of manufacturers using patent strategies to avoid price controls.

Other possible areas for reform cited by Mr Critchley include changes in the Board's regulations to speed up the price review process; changes to the Board's guidelines, particularly regarding price increases; and improved coordination with Canada's Common Drug Review.

Mr Critchley also identified a number of potential pitfalls facing policy development in Canada. One is the temptation to implement price controls best suited to countries governed by universal drug programs—such as New Zealand. In Canada's case, these measures could result in two-tier pricing. "If public plans negotiate secret rebates and better deals, does that mean that private insurers and cash-paying customers are going to be paying a higher price?" asked Mr Critchley. "That raises an important policy issue in our country, where so many people don't have access to public insurance. I think we should be sensitive to that question."

Canadian-American price gaps also place periodic pressure on Canadian drug prices. With the recent appreciation of the Canadian dollar, this issue has dissipated, but has the potential to re-emerge. There is also the ongoing tension between promoting innovation in drug development and ensuring affordable access to necessary medicines.

"And finally, but certainly not least important," Mr Critchley added, "is the question of the appropriate involvement of the public in general, and consumers in particular, in these decisions, which impact all of them and impact society as a whole."

Quality Use of Medicines

Lloyd Sansom *Chair, Australian Pharmaceutical Benefit Advisory Committee*

Lloyd Sansom opened the session by defining a drug subsidy as the start of a health outcome—not a health outcome in its own right. “We tend to get singularly focused at times on cost and availability, but not on what that does. One of the biggest challenges for us in Australia—and I think internationally—is not so much drug subsidy. It’s how we deal with behavioural change in stakeholders with respect to achieving the outcomes we know these drugs can get.”

Australia’s National Medicines Policy (NMP) was initiated in the late 1980s as a result of pressure from an Australian consumer association. However, it wasn’t until 2000 that the policy was in place—patience is a virtue in the pharmaceutical policy realm, noted Dr Sansom.

The NMP is designed to balance optimal health outcomes with economic objectives—in other words, to get better health outcomes through better use of medicines. The policy has four main goals: equitable access to necessary medicines; medicines that meet high standards of quality, safety and efficacy; quality use of medicines; and a viable and responsible local pharmaceutical industry (Figure 3).

Quality, safety and efficacy of drugs are the responsibility of the Therapeutic Goods Administration, Australia’s drug registering authority. Drugs can’t be subsidized unless they are registered—and registered for the specific indication for which they will be subsidized.

Balancing health needs and fiscal realities requires access to necessary medicines at a cost that the individual and the community can afford, particularly in the context of new high-cost drugs and Australia’s aging population. Access must be as simple and streamlined as possible, noted Dr Sansom, so that subsidization of medicines is timely, mechanisms are understood, and unnecessary administrative barriers and expenses are avoided. Financing arrangements must avoid encouraging cost shifting between levels of government or other funders, or other incentives that perverse the spirit of the policy.

Four structures support the NMP. The Australian Pharmacy Advisory Council consists of representatives of all stakeholders—consumers, industry, government (both state and federal), health professionals, and the media. The council oversees the NMP and advises the minister of health. “If you don’t have such a committee, I strongly advise you to get one, because it has been absolutely paramount in pushing forward and profiling the National Medicines Policy in Australia,” advised Dr Sansom. “People need ownership, and you can only give them ownership if you make them part of it.”

The NMP is also supported by: the National Prescribing Service, funded by, but independent of, government; the Pharmaceutical Benefit Advisory Committee (PBAC), which advises on the subsidized listings of the National Prescribing Service; and an expert advisory group that oversees the quality use of medicines.



Figure 3

QUM and the National Medicines Policy

Reproduced from presentation slides, Toward a National Pharmaceuticals Strategy, 2006.

Australia's NMP defines quality use of medicines as the judicious selection of treatment options, including the choice between drug, non-drug and no treatment; appropriate choice, when medication is required, within and across drug categories; and safe and efficacious use. The policy assumes that quality use of medicines can be achieved through a multi-level, multi-strategic, systems-based approach that engages all stakeholders as active partners.

As part of this effort, Australia's National Strategy for Quality Use of Medicines has developed a number of important tools, including indicators, guidelines and standards to govern prescribing activities. The Strategy recognizes that changing behaviour and developing partnerships is a key part of achieving quality use of medicines.

Dr Sansom believes that the biggest success in the NMP system may be the National Prescribing Service, which works to support the quality use of medicines among all stakeholders. To achieve its mission, the Service uses nationally coordinated approaches: independent information about medicines; cross-discipline and cross-sector collaborations; a regular newsletter; a prescribing practice review; national call-in services for professionals and consumers; and educational print materials for consumers.

The Service has also developed prescribing curricula for medical, pharmacy and nursing schools specifically addressing quality use of medicines. This and other measures have brought about a shift in the focus of the pharmacy profession in Australia: "It's not supply of pharmaceuticals, it's quality use of medicines," Dr Sansom noted. "That's its *raison d'être*. That's its future. That's its focus."

However, despite these institutional measures, work remains to be done. As Chair of Australia's Pharmaceutical Benefit Advisory Committee, Dr Sansom remains frustrated that recommendations for coverage are made on the basis of clinical trials, without knowing whether the desired outcome is actually achieved in practice. So PBAC has begun to ask industry to think about quality use of medicines when they make their submission, and to identify the factors they think will affect the achievement of desired health outcomes in practice. Accordingly, the next step is to link utilization data with outcome data.

Packaging, labeling and drug names remain issues—and significant causes of adverse outcomes. All need to be taken into account in the registration process. Dr Sansom

would also like to see continuing improvements in PBAC's transparency, through explanations of the reasons for its decisions, an evidence-based approach, and the promotion of quality use of medicines as part of drug selection.

The price of drugs will continue to go up, and maintaining equity will require serious public financial commitment. Maintaining sustainability will require effective expenditure management. Cost-effectiveness and quality use of medicines, Dr Sansom said, are major keys to achieving both goals.

Robyn Tamblyn *Professor, McGill University, Canada*

Between five and ten per cent of hospital admissions are a result of adverse drug-related events. Almost half are preventable—caused by prescribing errors, sub-optimal drug management, or under-use and over-use of treatments. On the other side of the equation, unavoidable or unpredictable adverse events can potentially be addressed through pharmaco-genomics and other approaches, which ideally should be part of a post-market surveillance program. Whatever the root cause, the direct health care costs of an adverse event are approximately \$5,500.

A study by Robyn Tamblyn that followed 21,000 people in a typical urban area in Montreal found that only 27 per cent had a single prescribing physician. Only 59 per cent used a single pharmacy. Multiple prescribing physicians and multiple dispensing pharmacies increase the risk of inappropriate prescriptions, because no single person has a complete picture of the care being provided to the patient. Another study found that handwritten prescriptions create problems in pharmacist transcriptions in about 15 prescriptions out of 100, 1.5 of which could cause serious harm.

Optimizing drug therapy has several requirements, noted Dr Tamblyn. "There is no single silver bullet. We need a complex approach to this, a complex set of solutions."

The first step is safety. Anyone prescribing or dispensing drugs should have complete information on all the drugs a patient is receiving, and prescribing and transcription errors must be reduced. The second step is to improve the match between need and therapy, and enhance compliance with treatment. And the third step is to improve the cost-effectiveness of the treatment, by using the least expensive drug to achieve the desired outcomes.

A 1998 study showed that the use of computers in hospital prescription systems reduces not only medication errors but also adverse events. However, solutions are more challenging for primary or ambulatory care, where most drugs are prescribed.

Much of Dr Tamblyn's session described Medical Offices of the 21st Century (MOXXI), a mobile electronic prescription management system which launched across a population of 32 physicians, 39 pharmacies and 19,800 patients in Montreal.



Robyn Tamblyn, McGill University

MOXXI enables physicians to electronically send pharmacists therapeutic information in a prescription, and in turn allows pharmacists to send physicians information on all drugs dispensed. The system automates as much of the process as possible: patient data is preloaded from the province's medical insurance program onto physicians' handheld computers; available drug selections are listed in a menu; and reasons for prescribing a particular drug are also listed. The system alerts the physician if it detects any problem with a prescription, and the physician can send the pharmacist a stop order (to stop refilling a prescription) along with reasons for the order. The computer tracks all current medications prescribed for a patient, and identifies prescriptions that haven't been filled. To avoid transcription errors, nothing is typed—everything is selected from preset lists.

In order for the system to be successful, the technology has to work, and Dr Tamblyn noted that hardware and software has to become more stable in order to support this type of real-world, real-time effort. MOXXI also has

to fit into physicians' workflow—in primary care, where physicians see a patient for an average of seven minutes, this means the system has to be fast.

Early results from the trial have been positive. Interestingly, physicians perceive printed (as opposed to handwritten) prescriptions as the greatest benefit of the system, followed by the drug profile information and the rapid refilling functionality. Physicians tend to involve patients with complex medical needs—those most likely to benefit from improved prescribing. They also use it for their most vulnerable patients—those with the lowest income—because physicians typically have the most difficulty obtaining a reliable medication history for these patients.

“The good news here is that these are the people who are much more likely to be hospitalized in our country as a result of drug-related problems,” Dr Tamblyn said. “The physicians are using the system strategically.”

MOXXI is also providing valuable information about why certain drug groups, such as psychotropics, are being prescribed, and whether they are being over-prescribed. “It begins to be a risk management strategy that can be used in pharmaco-surveillance,” Dr Tamblyn added. Results also indicate that stop orders are occurring in about seven per cent of cases—and about two-thirds of those stop orders are related to ineffective treatment or adverse drug effects. In other words, the system could play a key role in reducing inappropriate prescriptions.

Could the system be used to provide disease decision support? The initial stage of the MOXXI project focused on asthma—a growing problem in which sub-optimal prescribing patterns appear to be the norm. The system provides a ‘dashboard alert’ for the treating physician, identifying asthmatic patients who are over-using fast-acting bronchodilator. It also displays patient histories, and outlines recommended treatments.

“So it's basically embedding guidelines right into a point-of-care system that makes it really easy to do the right thing, which is really our bottom line,” concluded Dr Tamblyn. The next step will be to provide physicians with cost-effective comparators when they are making a prescription—giving them a better idea of the actual costs of the therapy.

Drug Promotion and Quality Use of Medicines

Barbara Mintzes *Therapeutics Initiative and Centre for Health Services and Policy Research, University of British Columbia, Canada*

Barbara Mintzes opened the session by offering some international perspective on drug promotion regulation. A 2003 World Health Organization survey of national governments found that 109 countries (57 per cent) had laws in place governing drug promotion, and that 89 countries (46 per cent) actively regulated promotion.

Canada is close to the norm in terms of overseeing drug promotion, relying mainly on industry self-regulation. Health Canada is ultimately responsible for upholding Canada's Food and Drugs Act, but steps in only where there is a perceived risk to public health, or when industry has not complied with its self-regulatory bodies.

Specifically, noted Dr Mintzes, Canadian law prohibits deceptive and misleading advertising, direct-to-consumer ads for prescription drugs (except name, price and quantity) and ads for the prevention or treatment of very serious diseases listed in a special schedule of the Act. Advertising is broadly defined as including "any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device."

But advertising accounts for just a fraction of pharmaceutical promotion budgets. Additional types of promotion include: funding opinion leaders; sponsoring patient groups, institutes and health professional societies; gift giving; sponsoring continuing medical education, symposia and conferences; Phase IV market seeding research; and public relations, advertorials and ghostwriting. Promotional spending on prescription drugs in the United States totaled \$21 billion in 2002 (Figure 4). In Canada in 2004, it totaled \$2.1 billion—approximately \$30,000 per physician.

The five top drugs in terms of advertising spending in Canada in 2000 were Vioxx, Celebrex, Effexor, Lipitor and Baycol. Two of these drugs (Vioxx and Baycol) have been withdrawn from the market due to safety concerns. "One of the concerns about drug promotion is that it tends to focus on the newest products," Dr Mintzes said. "And often products are withdrawn or subject to serious safety warnings within the first two years of marketing."

Dr Mintzes cited drug ads—including some that had been prescreened through a voluntary process by the Pharmaceutical Advertising Advisory Board—that promote treatment at odds with clinical and public health guidelines.

An ad promoting clarithromycin (Biaxin) as a daily treatment for acute ear infections seems designed to expand use of the drug beyond those recommended by guidelines (the United States Centres for Disease Control recommend against routine antibiotic treatment of uncomplicated childhood ear infections—if antibiotics are needed, amoxicillin is the first choice).

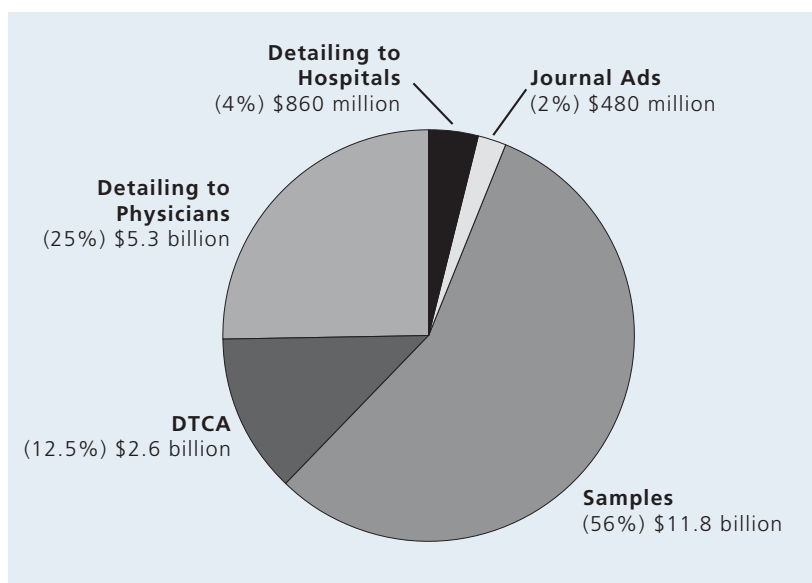


Figure 4

US Promotional Spending on Prescription Drugs (2002). Total Spending: \$21 billion.

Reproduced from presentation slides, Toward a National Pharmaceuticals Strategy, 2006.

Examples also included an unbranded ad by Hoffmann-LeRoche for Xenical (also Orlistat)—a drug approved as a treatment for patients who are very overweight and at extra risk for cardiovascular disease. Dr Mintzes pointed out that the ad in question targets women who want to lose a few pounds, not the seriously obese. “That has implications in terms of cost—not only in terms of drug prescribing but also in terms of stimulating physician visits by patients who don’t have a serious illness, who might not visit the physician otherwise.”

Ads also often don’t take into account cheaper alternative treatments, and sometimes even include fine print stating that dosages used in drug comparisons are dissimilar. Much of the persuasive power of these ads, noted Dr Mintzes, resides not in the words, but in the images used.

But what do we know about the effects of drug promotion? A 2001 American Journal of Medicine survey found that only one per cent of internal medicine residents stated that sales representatives greatly influence *their own* prescribing decisions, while 51 per cent stated that representatives greatly influence *other* physicians’ prescribing decisions. “There tends to be an under-acknowledgement of the extent to which one’s own practice might happen to be affected,” noted Dr Mintzes.

The only systematic review conducted of studies on interactions between the pharmaceutical industry and physicians showed a negative impact on knowledge, attitudes and behaviour. The only positive outcome identified was that physicians who attended lunchtime pharmaceutical sales presentations developed a better knowledge of treatment protocols for the complicated illness that was discussed, but had less knowledge of treatment of mild illness.

A more recent study in the United Kingdom looking at first prescriptions for a list of newly launched drugs found that the most frequent source of initial information was the pharmaceutical industry (49%). Peer-reviewed medical journals were rarely the source of information (1%). A sales representative was reported most frequently (39%) by physicians as the factor that influenced a prescribing decision, followed by suboptimal current therapy (25%) and patient requests (22%).

An ongoing French survey looking at drug information provided to physicians reported that in the majority of cases, sales representative did not spontaneously report adverse effects (32%), contraindications (31%), drug interactions (27%) or unapproved indications (31%). However, almost half (45%) of the physicians surveyed reported experiencing some degree of pressure to prescribe.

But there are solutions, and Dr Mintzes identified a number of potential aims for the regulation of drug promotion. They include: avoiding unnecessary harm; promoting quality use of medicines; removing financial incentives from treatment decisions; ensuring that prescribing decisions and drug use are based on complete, accurate information; promoting cost-effective care; and supporting ethical marketing standards and a marketplace aligned to health needs.

However, there are many barriers to effective drug promotion regulation. Dr Mintzes concluded by summarizing these as: “inadequate resources, no active monitoring, no effective sanctions, no prevention of repeat violations, no evaluations to see what is effective, and a certain lack of political will or a view that it really isn’t something to be taken seriously.”



Barbara Mintzes, Therapeutics Initiative and CHSPR, UBC

Drug Safety Regulation

Terence Young *Chair, Drug Safety Canada*

Terence Young's daughter, Vanessa, died in 2000, two weeks before her sixteenth birthday. She had been taking the prescription drug Propulsid (typically used to combat gastroesophageal reflux disease) sporadically for two years, and died as a result of its use.

Propulsid was taken off the United States market three days after Vanessa's death, and off the Canadian market five months later. At the time, it had caused a reported 80 deaths and 340 adverse drug reactions in the form of heart arrhythmia. The official number of deaths is now 302—Mr Young believes the number may actually be in the thousands.



Terence Young, Drug Safety Canada

Propulsid became a blockbuster. Yet the dangers of the drug were shown pre-market—eight children on Propulsid had died before it was approved in Canada in 1990 and in the United States in 1993. The drug's label was changed five times to include additional warnings through the 1990's as the number of deaths increased. Meanwhile, use of Propulsid grew, with sales reaching \$1 billion a year.

By 2001, noted Mr Young, the drug had 100 contraindications, including grapefruit juice, and was known to

be dangerously dose sensitive. Multiple warnings were issued in the United States, including a 'black box' warning, yet contraindicated use declined by only two per cent. No effective warnings were issued in Canada. Johnson and Johnson, who sold the drug through Janssen-Ortho, continued to promote it for off-label use.

An article in the New York Times, published in 2005 after the ensuing class action suits in the United States were settled, revealed that dozens of post-market studies indicating the drug's risks had not been made public.

The most common side effect of Propulsid—experienced by approximately ten per cent of patients in clinical trials—was diarrhea. However in 1998, the drug's label in the United States was changed to indicate that individuals experiencing severe vomiting or diarrhea should not take Propulsid because it could cause heart arrhythmia in patients with an electrolyte disorder. The drug was essentially contraindicated for itself, putting the lives of one in ten patients taking it at risk. Propulsid is still sold worldwide.

All drugs cause adverse reactions, and any drug has the potential to harm patients. Mr Young quoted Eli Lilly, founder of Eli Lilly and Company, as saying, "Any drug without toxic side effects is not a drug at all." The only difference between a drug and a poison is dosage.

Adverse reactions to prescription drugs are the fourth leading cause of death, said Mr Young. Thirteen major drugs, including Propulsid, have been pulled off the market since 1997 in the United States. In Canada, 41 drugs have been pulled off the market since 1960. "Drug companies have a whole lot of ways of covering up a serious adverse drug reaction," Mr Young said. "They say it's a brand new contraindication, we didn't know about that. Or they say that it's an overdose. Or they say that the data was flawed."

Over half of a drug's serious side effects won't be revealed pre-market. "If you test the drugs on 2,000 or 3,000 patients and then put them on the market and all of a sudden you've got millions of patients taking them, that's when the rare but serious side effects show up," Mr Young said. "And some of the smartest doctors I know don't recommend any drug for a patient and don't prescribe it until it's been on the market for five to seven years for that very reason."

Mr Young also quoted Dr Alan Roses, a senior vice-president at GlaxoSmithKline, as saying: “Most prescription drugs work half the time or less.” The conclusion stemming from this is not very reassuring, argued Mr Young. “You don’t know what the risk of the drug is until it’s been on the market for years and millions of people have used it. And yet in many cases there’s absolutely no benefit for many patients. So it means thousands and perhaps millions of patients are taking drugs with no possible benefit and a very real risk.”

How do we protect patients from the potential harm posed by prescription drugs? Mr Young believes the current ban on direct-to-consumer advertising in Canada should remain in effect. The precautionary principle must also be protected, to prevent it from being overridden by risk management (the corporate practice of managing the risk of being sued). Mr Young also argued that cause and effect (the standard used by coroners when investigating a death) is too demanding, and often allows companies to avoid responsibility. Canada should adopt the Norway Rule, which sets out the principal that new drugs should not be approved until they have been shown to be more effective than existing drugs.

Mr Young ended his session by offering some advice to physicians as they attempt to tackle issues surrounding drug safety and quality use of medicines: demand truly effective warnings in plain language; read the small print; reject off-label promotion; give patients the facts about manipulation in direct-to-consumer advertising; reject gifts and debts of gratitude; and report all adverse drug reactions to Health Canada.

Mary Wiktorowicz Associate Professor,
York University, Canada

Drug regulation is not an entirely objective or scientific process. It attempts to balance the goals of public health with the timeliness of the approval process. It deals with considerable uncertainty—no drug is without risk, and the criteria used to judge what is safe and effective can be subject to negotiation. It also deals with scientific constraints—regulatory agencies don’t have complete independence, and must rely on the results of clinical trials entrusted to private sector actors.

Perhaps most strikingly, different political traditions and institutional histories lead to varied regulatory arrangements. Mary Wiktorowicz’s research has compared drug regulatory processes in Canada, the United States, Britain and France to illustrate how different nations’ interpretations of public authority shape regulatory approaches.



Mary Wiktorowicz, York University

In all regulatory environments there is tension between government and industry, and these dynamics lead to the evolution of different processes. Dr Wiktorowicz refers to the American approach to developing regulatory policy as *managerial discretion and adjudication*. When the Food and Drug Administration (FDA) develops regulatory policy, industry is not always formally represented—though it has the opportunity to offer feedback through review and comment processes, or can use the judicial system to appeal decisions.

Britain and France use a corporatist approach to developing regulatory policy—both countries have a tradition of state-society relations in which industry and labour organize into representative hierarchies that associate with government. It is assumed that industry has a role to play, and because the regulatory agencies in Britain and France have fewer resources than their American counterpart, they adopt a more consultative approach to ensure compliance. Dr Wiktorowicz referred to this style of developing regulatory policy as *bargaining*.

Canada has gravitated toward a combination of the American and European approaches, adopting some aspects of managerial discretion but also consulting with industry fairly extensively.

The FDA's process is the most open. Freedom of information legislation and related measures in the United States ensure the rationale behind a particular drug approval is made public. Proceedings of expert advisory committee meetings are publicly available. In contrast, in Canada, Britain and France, the proceedings of expert advisory committee meetings and approval rationales are not made public.

Another key difference among these institutional approaches relates to the concentration of power. The FDA is subject to oversight by congressional committees and hearings, which frequently call it to account for its actions. This in turn orients the FDA to take an adversarial stance toward industry. In Canada, Britain and France, noted Dr Wiktorowicz, there is less legislature oversight, allowing power to be more centralized and regulatory agencies to have more independence in choosing and implementing policies. These different approaches affect regulatory standards. For example, the FDA reanalyzes randomized controlled data that are submitted by companies, in contrast to the other three countries, which review summary data.

However, Dr Wiktorowicz noted that all four countries face common limitations. Conflict of interest on expert advisory committees is a key concern—regulatory agencies in Canada, the United States, France and Britain all use experts to evaluate drug submissions, and these experts are often the same individuals drug companies use to conduct clinical trials.

Timeframes for trials and approvals are also under international pressure. The duration of randomized controlled trials has already been reduced from 12 to six months—an issue in terms of catching the long-term effects of new products. There is also pressure internationally to reduce the length of approval processes. Standard product approvals in the United States require 12 months, while priority fast-track approvals take six months. Approval times in Britain are 44 days. Faster approvals, however, tend to increase the rate at which products are withdrawn from market. The United States has a lower withdrawal rate (3% to 5%) than Britain (6% to 10%). The rate of withdrawal in Canada is only two per cent—not because of rigour but because of slowness, argued Dr Wiktorowicz. As Canada's process is slower, it affords regulators the opportunity to see any adverse events in other countries before making a final decision.

External factors also affect the regulatory process. Globalization's emphasis on industrial competitiveness is streamlining and weakening regulatory criteria. Dr Wiktorowicz also noted that the harmonization of regulatory standards around the world—such as the development of international criteria for carcinogenicity and toxicity testing—typically involves adopting the *least* stringent national standards.

A significant challenge all regulatory systems face is the limited usefulness of pre-market testing in evaluating safety. It is counterintuitive that as the use of a new drug increases exponentially on market entry, its effects and patterns of use are no longer systematically monitored. In addition, argued Dr Wiktorowicz, passive reporting of adverse drug reactions is not effective—it tends to be slow, expensive and incomplete.

So complementary post-market surveillance is needed. However, Dr Wiktorowicz noted that the completion rates of post-market studies are problematic. In the United States, only 46 per cent of post-market Phase IV studies requested as part of the FDA's accelerated approval process are completed, because companies are not legally required to do so. A study in Britain found that company-sponsored post-market studies suffered from weak study design and difficulties in recruitment. Strategies for addressing these problems could include making drug company patents and drug plan reimbursement dependent on completion of post-market safety and effectiveness studies.

Nonetheless, several post-market surveillance initiatives are underway. Britain has launched physician surveys on the first 10,000 patients who use a new product, and is maintaining a general practice research database. France is linking drug reimbursement to the results of Phase IV trials. The United States has commissioned studies to analyze health databases through the Centres for Education and Research on Therapeutics, launched electronic filing of adverse drug reactions, and created a new Drug Safety Oversight Board. Drug companies also have a role to play—including the creation of online registries to collect safety data, and the funding of arms-length, post-market surveillance studies.

But these efforts can be pushed farther, and Dr Wiktorowicz offered several suggestions for improving post-market surveillance in Canada: expand the Notice of Compliance, currently used only for accelerated approval, to the standard approval process; establish a network of research centres empowering Health Canada and provincial drug programs to commission post-market safety studies; fund a research network with the capacity to link public drug databases with medical and hospital records in order to conduct observational post-market studies; establish an expert advisory committee, with representation from provincial drug plans, to advise Health Canada on the types of post-market studies that are needed for each new product.

“Finally, I think we have to stop thinking of the regulatory process as a black box and think of it as a continuous stream,” Dr Wiktorowicz concluded. “Once products are on the market, we still need to look for evidence of safety. We need a system in Canada where greater oversight takes place.”

Robert Peterson *Clinical Professor, Faculty of Medicine, University of British Columbia, Canada*

Robert Peterson opened his session by citing a key challenge in drug safety regulation: “Getting innovative new therapies into the health care delivery system in a timely, cost-effective fashion, while having a system in place that ensures safety to the greatest extent possible.”

Most clinical trials used in the drug development process are powered to determine efficacy, not safety. Authorization is based on a positive benefit-to-risk profile where there is evidence of a specific benefit in a carefully controlled group of patients, and safety is assumed on the basis of an absence of evidence to the contrary. In addition, noted Dr Peterson, safety is a relative term.



Robert Peterson, Faculty of Medicine, UBC

Current drug approval regulations in North America and Europe are heavily focused on preclinical development. “It’s not necessary to show that a new product is safer or more effective than one that is presently on the market,” Dr Peterson said. “It’s simply necessary to show that it’s at least as effective as the product on the market.” Regulations require substantive evidence of safety, efficacy and quality within the narrow range that a drug is being approved for.

“There is no question, based on the exciting therapeutic options that have been developed in the past one to two decades, that regulators are committed to early market

entry of promising new therapies,” Dr Peterson said. “And clearly regulators are compelled to make decisions based on limited data. The basis of the pre-market randomized controlled trial scenario does limit the amount of data that one will have.”

Do the current international regulatory requirements adequately address safety? Dr Peterson believes the answer is both yes and no. About 78 per cent of new drugs make it through the pre-market testing providing a fairly accurate view of how the product will do in post-market. But approximately 20 per cent have important safety issues raised in the post-market, and another three per cent end up being withdrawn because of very serious—catastrophic for patients—safety issues arising in the post-market.

Given the amounts invested in drug development, Dr Peterson feels a three per cent failure rate is unacceptable. He also noted that these issues probably wouldn’t be detected in a typical clinical trial. Detecting a one-in-10,000 serious adverse drug reaction would require a clinical trial involving about 30,000 subjects—in reality, trials involving 5,000 patients are considered large.

Canada and several other countries use Phase IV commitments for many market authorizations. Canada also uses drug authorizations with conditions, known as a Notice of Compliance with Conditions. European countries have the flexibility of two additional options that don’t currently exist in Canada: formal conditional authorization, which allows for an annual review of products, and authorization under exceptional circumstances. Both categories recognize the fact that clinical trials are relatively lacking for certain products.

Phase IV studies are frequently required to validate efficacy identified in Phase III trials—they are also often used to extend safety evaluation. They are not regulated in Canada or the United States, and are often not completed (in fact, they are often not *started*). Nonetheless, market authorization continues despite the fact that Phase IV study commitments have not been met.

Dr Peterson pointed out that virtually no post-market regulatory authority exists in North America. If a product receives a Notice of Compliance, and a regulator believes that an important safety statement needs to be added to the product monograph, there is no regulatory authority to compel that change.

Authority only exists to remove market authorization. There are no regulations governing Phase IV trials or off-label use.

To address these issues, Dr Peterson believes that food and drug regulations should be amended to govern Phase IV trials. Regulations are needed for the provisional licensing of new drugs. Periodic safety reports based on international data should be required to be submitted, reviewed and summarized for publication. A policy is also needed for off-label use of new drugs.

Dr Peterson also argued for the development of regulated educational materials regarding all new drug products. “There are no formal, structured educational materials that are available to prescribers at the time that a new drug comes onto the market in the United States, in Canada or in Europe that will allow that prescriber to understand exactly what the benefit-to-risk profile was that brought the drug to market. It’s absolutely absurd that an individual is going to be able to competently prescribe a new medication based upon the relatively restricted text that exists in a product monograph.”

Finally, Dr Peterson called on Health Canada to expand the scope of its oversight role. “Drug safety is finding a new prominence for which drug regulators and drug developers are ill prepared. Health Canada needs to modernize its authority to regulate beyond the narrow pre-market and approval phases of drug development.”

Real-World Evaluation of Safety and Effectiveness

Morris Barer *Scientific Director, Canadian Institutes of Health Research Institute for Health Services and Policy Research, Canada*

Morris Barer opened the conference's safety and effectiveness session by outlining plans under development by the Canadian Drug Policy Development Coalition (CDPDC), a group pursuing a proactive approach to the lack of systematic post-market scrutiny of drugs, and to the disconnect between information on the real-world effects of new drugs and drug policy.

The recently formed CDPDC is currently a loose coalition of researchers, decision-makers involved in regulatory or funding decisions, consumer representatives, and representatives from agencies such as Cancer Care Ontario. The Coalition is working in collaboration with the National Pharmaceutical Strategy, developing a business plan, and assembling potential funding partners.

The current vision being proposed by the CDPDC has three key elements. The first focuses on oversight, direction and accountability and, itself, has two parts—a policy advisory group that would identify priority areas for research, and a scientific advisory group that would help determine how to best answer the questions raised by the policy group.

A second element would involve surveillance and evaluation research. The surveillance component would be designed to address the current serious underreporting of adverse drug reactions in Canada by building a systematic and comprehensive process of reporting. Evaluation research would involve creating a network of research centres. The faculty and staff of these centres would: undertake observational research on the use and effects of new products; oversee real-world effectiveness and cost-effectiveness trials of much broader scope than those currently run in the pre-market period; respond to ad hoc requests for information; and undertake syntheses of existing evidence.

Finally, the CDPDC envisions a comprehensive knowledge translation and exchange strategy, including continuous interaction with prescribers and pharmacists, to ensure that up-to-date information emerging from the network is properly disseminated.

“This proposal would have beneficiaries right across the spectrum—the federal, provincial and territorial governments, industry, health care providers, and patients,” Dr Barer said. “There will be something in this for everyone.”

But Dr Barer noted that any endeavour involving post-market surveillance faces challenges in Canada. Only three provinces systematically collect population-wide prescription data—and even in these cases researchers often have difficulty accessing the information. In addition, there is limited capacity to track and link prescription use in hospitals to prescriptions made outside of hospitals.



Morris Barer, CIHR IHSPR

“Canada, of course, has a worldwide reputation for its data resources—a function of the way that health care is funded in the country,” noted Dr Barer. “But when you actually start to look at the challenges of post-market surveillance, there is reason for pause.”

Dr Barer also expressed concern about the research community's lack of involvement in the development of the electronic health record: “Right now, it's not being designed with extraction for research purposes in mind.” The type of information required for true post-market surveillance will include hospital data, physician contact data, and potentially, data on alternative health product use. “We don't need comprehensive information everywhere. What we want to have is the capacity to pull together the evidence that is fit for each purpose.”

Few of these challenges are insurmountable, and none are fatal, argued Dr Barer. He identified the keys to effective pharmaco-surveillance as information system development and improved access for research and surveillance. The federal, provincial and territorial governments, in turn, hold the keys to moving forward in these areas.

“We should be moving toward comprehensive ambulatory prescription drug information systems in all provinces, linkable to other data sources and from which we can pull outcomes or side effect information.” It will also be important to harmonize and facilitate access protocols for research if a coordinated research network is to be able to provide timely responses to requests for research. Inter-provincial standards and data-sharing agreements will be vital.

Dr Barer also recognized funding realities. Public investments in large real-world trials and research infrastructure are crucial, although this doesn't mean that jurisdictions should be duplicating efforts. Any comprehensive funding model should include sufficient resources for training, development and refinement of methods, observational and trial-based surveillance research, and timely knowledge translation.

Finally, Dr Barer laid out other factors critical to the success of an effective post-market surveillance initiative such as the one being developed by the CDPCD and the National Pharmaceutical Strategy: involvement of policy-makers from the outset; timely response capability and good science; timely access to necessary data and resources; independence and transparency of surveillance activity; and, most importantly, willingness and ability to act in a timely fashion on surveillance-generated evidence.

Bruce Carleton *Director, Pharmaceutical Outcomes Program, Children's and Women's Health Centre of British Columbia, Canada*

Bruce Carleton continued the session by outlining the true costs of incomplete knowledge of drug outcomes. There is the cost of drug utilization, which is increasing rapidly in Canada. There is the cost of failed treatment—the failure of a drug therapy to achieve its desired outcome. And most dramatically, there is the cost of adverse drug reactions. Complicating these issues is individual variability in drug response, which can result in very serious negative consequences.

“Drug use is a balance between the effectiveness component and the harm component,” Dr Carleton said. “So we need to understand both costs.”

Unfortunately, we don't understand what drug outcomes are achieved with new drugs when they come on the market, argued Dr Carleton. For the most part, drug outcomes are determined in the post-market.



Bruce Carleton, CWHCBC

For example, a number of therapies are available to reduce the risk of bone fractures in osteoporosis patients. Two common treatments, bisphosphonates and teriparatide, cost up to \$700 and \$10,000 a year, respectively. But there is no evidence that teriparatide is an effective treatment for patients for whom the less expensive bisphosphonate therapy doesn't work. What is the incremental benefit of using a \$10,000-a-year therapy

over another therapy that costs significantly less? “I think that’s an important question to ask, and I think it’s reasonable to get an answer to that with a properly designed trial,” Dr Carleton said. “We don’t have that evidence, despite the fact that both of those drugs are on the market.”

So the quandary: adverse outcomes are significant, but specific predictors are unknown. Life-threatening or high-morbidity illnesses may require the use of less-understood drugs, and the scientific determinants of drug response are not necessarily obvious or available.

The pharmaceutical industry’s drug development model also presents problems. Clinical testing is required on ten drugs in order to get one approval—a situation that Dr Carleton called inefficient. This high failure rate drives drug development costs up.

“In the old days, we used to refer to blockbuster drugs as those that were going to be used in large segments of the population, and they were the drugs that the pharmaceutical industry could rely on to generate revenue sufficient to sustain the high development costs of drugs. But we have fewer blockbusters now. And fewer blockbusters mean that investors of publicly traded companies—the pharmaceutical companies—[become] cautious investors who wonder how they’re going to sustain drug development costs, and that results in some measure of under-capitalization.” This has become a significant problem for the pharmaceutical industry, noted Dr Carleton, one that isn’t easy to solve.

In terms of drug safety, Dr Carleton cited the example of Vioxx. None of the passive or voluntary adverse drug reaction surveillance systems in place were able to quantify and alert us to the cardiovascular risks the drug presented.

“Instead of blaming Merck and the regulators and the drug for this problem, I ask the question: What about the clinician’s responsibility to adequately monitor patient drug experience?” argued Dr Carleton. “We’re very fortunate with prescription drugs to know that most adverse effects are dose-related. That means that we can avoid the serious consequences of the most serious reactions by lowering the dose, and that requires a comprehensive plan for monitoring patients’ drug experience.”

The importance of post-market surveillance is well established, but Dr Carleton argues that active adverse drug reaction systems are needed in addition to voluntary systems in order to increase comprehensiveness. Post-market evidence of drug effectiveness (versus efficacy) is also required. Dr Carleton suggested that one way to achieve this is to focus on the rollout of drugs—paying for the drug and designing policy to produce evidence where critical data are lacking.

In order to produce evidence of drug benefit and safety, Dr Carleton argued, we need the inter-provincial network that the Canadian Drug Policy Development Coalition has been working to establish. Evidence-based, defensible policy is needed.

The inter-provincial network would produce evidence that can form the basis for cost-effective decisions about drug policy in the real world. The goal would be to make safety surveillance part of the clinical culture. Dr Carleton believes funding for this should be provided by the federal, provincial and territorial governments. Academic funding from the Canadian Institutes of Health Research and others is also needed, to ensure that the right group of experts is involved.

Dr Carleton concluded by reiterating that more evidence needs to be produced where critical information is lacking, and that a framework is needed for producing evidence by different methods. Observational data should be looked at, but scientific process and clinical trials in the post-market are also needed; variability in drug response is a critical issue that is not effectively dealt with through evidence-based medicine. And he also noted that the drive for pharmaceutical innovation could likely be hampered if criteria for market access are set too high.

“Finally,” Dr Carleton noted, “the goal, of course, is to make all of us as Canadians enjoy more effective, safe and efficient use of drugs.”

Geoff Anderson Professor, Health Policy, Management and Evaluation, University of Toronto, Canada

The conference's drug safety and effectiveness session was capped off with an overview of a Health Canada-funded study completed in 2004 that investigated the potential of incorporating pharmaco-surveillance into provincial formulary decision-making processes.

Geoff Anderson was the principal investigator on the Development and Evaluation of a Framework for Incorporating Pharmaco-Surveillance in Provincial Formulary Decision Making study, which involved researchers from the Therapeutics Initiative (TI) in British Columbia and from the Institute for Clinical Evaluative Sciences (ICES) in Ontario.



Geoff Anderson, University of Toronto

The study was designed to improve the links between researchers in both provinces, and improve links between researchers and decision-makers within each province. The study team worked with formulary decision-makers in Ontario and British Columbia to define priorities for pharmaco-surveillance evidence; developed and refined shared techniques for producing that evidence; and assessed the usefulness and impact of the evidence on decision making.

Dr Anderson noted the important distinction between regulators at the federal level, who decide whether to license a drug, and decision-makers at the provincial level,

who decide whether a drug should be funded. Regulatory or safety decisions are different than drug coverage decisions, and the study focused on drug coverage decisions at the provincial level.

The study team began by asking provincial decision-makers what type of evidence they used in making funding decisions. The answer was clinical trials, with a focus on cost-effectiveness evidence. Post-market monitoring was typically limited to determining budget impact. The study team then asked decision-makers to identify priorities for post-market study—the decision-makers in the two provinces agreed on a common set of priorities: COX-2 inhibitors, atypical neuroleptics, biologics, statins and proton pump inhibitors.

Next, the team offered provincial decision-makers an opportunity to use three different study types when investigating these priorities. A *descriptive study* would use claims data to describe how many people use a drug and how much it costs. An *appropriateness* study would identify not only how many people use a drug and how much it costs, but also the characteristics of the people who used the drug. The most comprehensive option, an *outcome study*, would also investigate outcomes associated with a drug—it could be used to look at safety and effectiveness.

Dr Anderson observed that while it is possible for researchers and drug plan administrators in different provinces to agree on priority areas and undertake research using common methods, managing ongoing input presented challenges. He suggested that regular, brief meetings between researchers and administrators could improve the usefulness and impact of pharmaco-surveillance evidence, and that a routine process for triggering studies could also be useful.

Another lesson can be drawn from the Health Canada study: “Local expertise is important,” Dr Anderson said. “You can’t send all the data to some central location like Toronto and have it analyzed and then have the results sent back to British Columbia. That just doesn’t work. The interaction between the decision-maker and the researcher is better done at the local level than at the national level.”

Pharmaco-surveillance evidence is also most useful when it is relevant and timely. Research evidence is relevant when it evaluates a specific listing decision or policy, and

is presented in a way that facilitates application. Research evidence is timely when results are available at the right time in the decision-making process—for example, in response to a defined post-marketing evaluation period.

The Development and Evaluation of a Framework for Incorporating Pharmaco-Surveillance in Provincial Formulary Decision Making study ended two years ago, and along with other studies funded by Health Canada on real-world safety and effectiveness, generated interest among researchers and decision-makers. Subsequent proposals have been submitted to Health Canada to fund ongoing work on post-marketing surveillance at the national level, but momentum has been lost in what Dr Anderson termed the federal-provincial-territorial-National Pharmaceuticals Strategy ‘morass.’ Some research continues at the cross-provincial level, but overall progress has slowed.

So while there is great potential for producing relevant evidence for decision making at the national level, there remain challenges. Dr Anderson described the need for a ‘receptor’ function within Health Canada, which understands the evidence and has the willingness and the mandate to act on it. Data sources need to be maintained and improved, and research talent is in desperately short supply. “Researchers are a very limited resource, and people who want to work with governments and decision-makers are at a real disadvantage in terms of their academic life.”

And finally, Dr Anderson advised: “We need to walk before we can run.” The goal is an overarching plan, but it might be best to begin with focused proof of concept studies. Dr Anderson suggested a potential target for just such a study: the risks associated with atypical neuroleptics. Despite the fact that these drugs are widely used, and despite concerns that they increase the risk of death in frail elderly patients, no definitive observation study has been conducted.

Pharmaceutical Policy Reform: The Road Ahead

Alan Maynard *Professor, University of York, United Kingdom*

Alan Maynard opened the final session of the conference by posing a fundamental question regarding pharmaceutical regulatory reform: “Has much changed in the last decade?” To his mind, the record of the past ten years is mixed. In some ways things have improved, but other things have been relatively slow in changing.

This led Dr Maynard to ask another question: “Why are we so slow—why do we stick with the status quo in so many ways?” Dr Maynard pointed to a trade-off between health and wealth. Society wants to spend money in a way that



Alan Maynard, University of York

improves the health of the population, but also wants a functioning pharmaceutical industry, which in turn wants to be profitable. Society wants to allocate resources on the basis of benefit per unit cost—in essence, cost-effectiveness. Its pursuit of health focuses on least cost, evidence of clinical effectiveness, and control of volume. Industry wants to produce drugs that are clinically effective and cost-effective, but it also wants to make a profit. But how much health, and how much wealth?

The pursuit of profit induces industry to be what Dr Maynard called ‘economical with the truth.’ This could include misrepresenting clinical effects, raising prices or, where

prices are controlled, manufacturing demand by encouraging off-label use, and ‘buying’ clinicians and economists to produce biased trials and poor peer review.

Dr Maynard also described some of the techniques used by pharmaceutical industry—as outlined by David Sackett and Andrew Oxman in a *British Medical Journal* article—to ‘corrupt’ the marketplace. They include: selective and non-systematic reviews of relevant literature; cherry-picking patients for trials; efficacious co-interventions to adjust the product during trial; over-interpretation of positive trials; selective reporting of results through ghostwriters; burying unfavourable results; widening the boundaries of medical conditions by exaggerating prevalence; and developing financial relationships with physicians and economists.

Furthermore, the industry’s reluctance to provide access to basic data and publish negative results affects the perception of efficacy. “You’re only getting half a view of what is going on in this marketplace,” Dr Maynard said. “There’s a lack of focus on the adverse effects of drugs. Surely these should all be listed and publicized, both from the initial trials and post-marketing.”

So how do we get what society wants? Dr Maynard believes that we have to be better at addressing these issues. For example, Dr Maynard asked why there isn’t an “international united front” against current efforts to reduce the duration of clinical trials from 12 to six months. “So all these games are there, and we know about it, and again, we’re reluctant to try and change it.”

There is also the challenge of determining cut-off points and limits. Institutions like the National Institute for Health and Clinical Excellence (NICE) are forced to be ‘rationers’—and rationing the allocation of technologies is difficult. “The politics of rationing is really quite difficult,” Dr Maynard said. “The politicians find rationing very difficult to handle in terms of their votes. And the medical profession is still obsessed with the individual perspective—doing what they can for the patient in front of them—rather than the social perspective.”

“But we’ve got to begin to ask questions about whether they should be price-takers or price-makers,” Dr Maynard said, citing NICE as an example of a price-taker and Australia and New Zealand as examples of price-makers. But again, Dr Maynard questioned whether politicians are ready to confront industry.

Another difficulty cited by Dr Maynard is that regulation is often designed and implemented to protect the regulated from competition—not to protect the consumer. And regulatory failure is creating worldwide fear about costs.

Finally, Dr Maynard called for ongoing change—a ‘continuing revolution.’ “There is a need for a continuing focus on what we know and improving the regulatory environment, and that goes against all the pressure for reducing regulation and having global trade. But if we’re really going to get the right trade-off between wealth and health, regulation has to be improved.”

Robert Evans *Associate Director, Centre for Health Services and Policy Research, University of British Columbia, Canada*

Robert Evans capped off the conference’s final session by referencing two expenditure slides presented on the first day of the conference by Penny Ballem (Figure 1) and Wayne McNee (Figure 2).

“What they tell you is that the escalation of drug costs is not a force of nature,” Dr Evans said. “It is not a tsunami. It is something that is socially constructed, and that can be socially controlled if there is a desire for it, and the mechanisms are there.” The other important lesson Dr Evans drew from the slides was a simple accounting reality: every dollar of expenditure is a dollar of someone’s income. Reducing projected increases in pharmaceutical spending in British Columbia would have a direct impact on the



Robert Evans, CHSPR, UBC

pharmaceutical industry's bottom line. "It is a simple fact of the way we count things, and therefore New Zealand is a disaster from the point of view of the industry."

Dr Evans noted that conflict between health objectives and private economic interests is far from new, quoting from the 1867 annual report of the New York Metropolitan Board of Health: "The health department of a great commercial district which encounters no obstacles and meets with no opposition may safely be assumed to be unworthy of the public confidence." In other words, Dr Evans said, "If you don't get opposition, you're not doing anything in this field."

"The industry is in business for a profit, or if you like, to enhance shareholder value," Dr Evans said. "They're not in business for your health. They're not even in business to make drugs. They're in business to make money, and if they get confused about that, they will very quickly learn about it from the capital markets."

For example, when a 2002 American National Heart Lung and Blood Institute report indicated that hormone replacement therapy substantially *increased* the risk of heart disease, stroke and breast cancer, Wyeth-Ayerst stock fell about 40 per cent, wiping billions off the company's market capitalization, and investors' portfolios. Similar difficulties have recently ensnared Merck, the manufacturer of Vioxx. The capital markets, noted Dr Evans, are not forgiving.

Corporate leaders are acutely aware of this, as illustrated by a Fortune magazine article ('Merck Strains to Keep the Pots a Boiling') profiling Merck some years ago: "Around the company's headquarters in Rahway, New Jersey, there is so much high-minded talk about the company's mission that one might be forgiven for assuming that you are dealing with an eleemosynary outfit. But this impression is quickly dispelled by one's first meeting with the CEO, Henry Gadsden, who is as dedicated a devotee of the bottom line as ever was."

The consequences of this devotion, Dr Evans noted, are spelled out in Joel Bakan's recent book *The Corporation: The Pathological Pursuit of Profit and Power*, which suggests that the behaviour of corporations, which have all the rights and privileges of legal persons, matches the characteristics of a sociopath. Bakan uses the definition of sociopath supplied by *The Diagnostic and Statistical Manual of Mental Disorders*: a person detached from a moral, cultural or social context.

"The corporation is simply an organizational structure with a single purpose, which is the return of profit," said Dr Evans. "Of course, companies are made up of people and most of the people who work in companies, including drug companies, are in fact moral beings."

However, noted Dr Evans, individuals are remarkably capable of accentuating the positive. "People do things and believe in what they do, and the people who work with drug companies probably believe that they're doing something important, too. And, of course, to some extent they are. There's no question about the benefits that we derive from drugs. So what you have is an amoral, profit-driven organization absorbing more or less moral people who have to spend time shutting their eyes."

How else can one explain the story presented by Terrance Young earlier in the conference, asked Dr Evans? That was not a story of error or lack of information. The manufacturer knew its products were killing patients, suppressed the information and continued to market the drug. That is the behaviour of an amoral, profit-driven entity.

So what can we do about this? A drug company itself is not corrupt. It is energetically and very successfully fulfilling the societal role assigned to it: maximizing shareholder value. But as Alan Maynard outlined, in pursuit of this goal, corporations often corrupt or neutralize organizations and individuals that stand in their way. And the pharmaceutical industry, noted Dr Evans, has the resources to do so: "It is very difficult to compete with raw, cubic money."

Any institutions or processes we design to align pharmaceutical industry behaviour more closely with the broader public interest require a defensive function, an internal intelligence mechanism that protects against penetration and corruption. Noting the contrast between Sir Michael Rawlins' call for flexibility and the rigidity of New Zealand's fixed-budget coverage system, Dr Evans also warned of the dangers inherent in flexibility: "Once you give flexibility, you open the door for corruption."

Dr Evans ended his session by sounding a cautionary note regarding the 'continuing revolution' model proposed by Alan Maynard. "Continuing revolution is very uncomfortable. So the disruption that is associated with the approach of continuing revolution may have to be balanced against the corruption that is associated with living in a world where corporations behave as they behave."

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