The Merck Frosst - Centre for Evaluation of Medicines policy conference
Held in conjunction with the Canadian Association of Population Therapeutics annual meeting

Building the Evidence for Enlightened Drug Policy

Chaired by Dr. Stuart MacLeod, Centre for the Evaluation of Medicines, McMaster University

FINAL REPORT

On April 13th, 2002, the Centre for Evaluation of Medicines hosted the second annual symposium on drug policy in Canada. Organized in conjunction with Merck-Frosst Canada Ltd., the series provides a provocative forum for debate on the issues that are shaping Canada s drug approval and reimbursement policies.

An exceptional faculty was assembled to look at particular challenges of building the evidence for enlightened drug policy. Speakers then addressed the concrete challenges faced in building clinical evidence, the broader questions of what impact new drugs have on our social and economic well-being, as well as how policy needs to change to deal with new drugs issuing from genomic and proteomic research. A panel representing physicians, patients and policymakers then described the real world challenges they face in using evidence in their decision-making.

Faculty:
Lisa Crawford, The Arthritis Society
Dr. Lisa Dolovich, McMaster University
Dr. Jean-Pierre Gregoire, Director of Health Economics, Merck Frosst Canada Ltd.
Dr. David Johnstone, QEII Health Sciences Centre, Halifax
Sarah Kramer, Department of Health, Nova Scotia
Dr. Frank Lichtenberg, Columbia University
Dr. Stuart MacLeod, Centre for Evaluation of Medicines
Dr. Paul Oh, Sunnybrook and Women s College HSC
Dr. Mark Poznansky, John P. Robarts Research Institute

Introduction

By Dr. Stuart MacLeod

Drugs are the fastest growing segment of overall health expenditure in Canada and we cannot underestimate the importance of drug therapy in the Canadian healthcare scene. Canadian Institute for Health Information (CIHI) data in 1999 estimated that roughly 15% of the Canadian healthcare expenditure was on drugs, a dollar value of $13.3 billion. In 2001, it was in excess of $15 billion.

The reasons behind the growth in drug spending are no mystery. We have an aging population and a growing overall population. As well, there has recently been enormous emphasis on evidence-based medicine and narrowing care gaps, which entail greater costs. But the major reason for the growth in drug expenditure is the simple fact that drugs work well. We have safer, more efficacious drugs and, as our science improves, increasing opportunities to individualize drug therapy. We have a vibrant, innovative pharmaceutical industry and a growing biotech industry. These companies are successful and are introducing new products at a prodigious rate. More drugs are being developed for a niche market to be used effectively in a highly individualized manner.

The increasing importance of drugs in medical practice and as a proportion of health care spending requires that we pay significantly more attention to the policies that govern their development and use. These policy conferences seek to address two main questions: Are we getting good value for the money that we spend on drugs? Are there things that we can do better that would lead to better outcomes?

Recap of the 2001 policy conference

The first annual policy symposium in this series, held in Banff last year, was entitled Pharmaceutical policies in Canada: Evidence-based or emotion-based? At that meeting, Dr. Stephen Soumerai from Harvard University stated what seems obvious but in practice is not: that drug policies should be evidence-based whenever possible. He recommended avoiding a silo approach, advised advocacy groups to be proactive rather than reactive in presenting positive solutions, and called for the creation of better working links between governments, insurers and research-based institutions to bring about better drug therapy.

He further advised researchers to become more actively engaged in disseminating their results, and recommended establishing multidisciplinary policy advisory groups that would include epidemiologists, economists and patient advocates.

Don Willison of the Centre for Evaluation of Medicines at McMaster University pointed out that public policies are usually based on a process of negotiation and bargaining, not on evidence alone. They are a blend of political wisdom or intuition, some evidence, and a large dose of values. In order for policy solutions to be successful, they need to be technically feasible, financially manageable, and administratively doable. He cautioned that the impact of new information would likely be incremental. He also felt that new research evidence needs to be introduced at an early stage in the policy-making process if it is to have influence, and that key decision-makers should be involved in the planning process of policy studies.

Jacques Lelorier of the University of Montreal described the bridge between epidemiology and health economics, focusing primarily on what compliance means for our health economic calculations. This is especially relevant in the management of chronic diseases, where persistence with therapy is required for assessments of effectiveness to be valid. He emphasized that resources spent on drug therapy are likely to be wasted if the drugs are used only for brief periods.

Alan Detsky stated that there was absolutely no role for economic analysis in licensing decisions. He felt that the Therapeutic Products Directorate and Health Canada should stick to their mandate of deciding whether a drug is safe and efficacious, and should not be considering what a drug is going to cost. He pointed out that the customers for pharmaceutical companies are no longer just prescribing physicians, but also, and primarily, third party payers: government, employers and insurance companies. Economic analyses must therefore meet the needs of those payers. Dr. Detsky cautioned that Canada lacks the human resources needed to carry out a review of cost effectiveness for every new therapeutic product, and suggested that rather than duplicating efforts province by province, we should support the idea of a national review committee. One year later, this view appears to be shared by the federal government and most of the provinces.

This year s symposium set out to tackle the issue of evidence itself: what evidence is needed to build drug policy and how is this evidence used by different players in health care? These questions are becoming increasingly important as we enter into an era of accelerated drug discovery based on genomic and proteomic research. Drug policy will be challenged to respond to a whole host of needs and constraints, from the economic well-being of our country to the budgets of our health ministers, to the health of patients. Knowing what evidence we need and finding ways to gather it is vital to supporting enlightened decision-making in this new era.

Building Clinical Evidence to Support Health Policy
By Dr. David Johnstone

The ICONS project in Nova Scotia is one of the most important examples to date of using health services research in the service of informed policy. The project name describes our ultimate goal: Improving Cardiovascular Outcomes in Nova Scotia. But while ICONS deals specifically with heart disease, its lessons will be applicable to other chronic diseases. Until April 1st, 2002, ICONS was a five-year study tracking the heart health of thousands of Nova Scotians. By looking at three of the common and major heart conditions -- unstable angina, acute myocardial infarction, and atrial fibrillation -- we were able to scorecard cardiovascular health in our province. The project involved 32 full time employees and a 76-member steering committee.

A living laboratory

Nova Scotia is a nice laboratory, with only one million people and nine well-defined healthcare regions. Halifax is the only tertiary care and university centre for the province, and people travel there from all other regions for heart surgery. ICONS has a well-oiled network in place, with a study coordinator nurse in each region, backed by a cardiologist who sets the agenda for that region. There is also a family physician and, importantly, a pharmacist involved. The ICONS steering committee does not necessarily control what each region does, but rather sets out a menu of options and an overall goal of improving cardiovascular health.

Regional teams participate in the collection and analysis of data which provides measurements of clinical quality improvement (CQI). That local involvement minimizes the resistance often seen with top-down CQI processes. Today, ICONS has one of the largest databases in the world measuring sequential quality of life. We have learned a lot from what our patients are saying. They consent to very detailed interactive educational events with us, tell us what is on their minds, and we send them information and materials on their cardiovascular health and include them in studies. Before discussing our findings, I will describe what it is we measure, how we measure, what we do with the information, and, notably, what all the stakeholders do with the information.

In order to define interventions to improve outcomes of heart attack, it is important to know the population we are dealing with. Two thirds of heart attack patients are male. One third of heart attacks in Nova Scotia are in people over the age of 80. Heart failure is the most common reason an adult is in hospital in the province of Nova Scotia and 51% of women with heart failure are over 80. In cardiovascular medicine, we have demonstrated that specialized clinics led by nurse-practitioners are very effective in keeping people with heart failure out of hospital. But given the population, we then need to ask who is going to drive the 83-year old woman to this highly effective clinic. The answer is nobody. The husband died nine years earlier, and she takes nine or 10 drugs a day. So access to even a great innovation such as a specialized heart clinic becomes a problem, and research priorities shift to areas such as tele-homecare, tele-health initiatives, and educational initiatives for the elderly.

We had some help from Quebec colleagues who run an asthma network in making our presentation of outcome ranking more politically acceptable. Rather than presenting regions or health units in order of first to last, our colleagues recommended using cartography, which is now an important presentation tool in ICONS. Among the four regions with the worst heart attack density in Nova Scotia, Cape Breton is roughly four and a half hours from Halifax, and Yarmouth three and a half. If we look at the 90-day cardiac catheterization rates between these regions as an indicator of outcome, we see that about one in two Halifax heart attack victims underwent cardiac catheterization by 90 days, as opposed to half that in these more distant regions. Odds ratios on various factors such as income and education were not found to have an impact. However, female gender, greater age and distance from the tertiary care centre did influence outcomes. Presenting these treatment patterns by using different colors appears to be more helpful than using a numerical rank.

Measuring improvements in care

Medication use was monitored every quarter before and after ICONS started feeding quality improvement information back to the regions. For acute myocardial infarction, aspirins, beta-blockers, ace inhibitors, and the statins are the big four evidence-based therapies. Appropriate prescription of aspirin reached levels comparable to those seen in the major US Infarct networks. There was also tremendous growth in the use of beta-blockers, which are inexpensive and keep people out of hospital. But perhaps as important as our actual results, the ICONS process resolves some of the key problems we face in getting evidence into policy making. Decision makers are aware of our research because they participate in two steering committee meetings a year where we examine what was learned in the past year and set priorities for the following year. Skepticism about the evidence is minimized because all parties participate in its collection.

Poor screening or diagnosis is an under-recognized part of the care gap in cardiovascular care, as was attention to co-morbidities. ICONS nurses in the regions scoured the charts of heart attack victims. In 50% of the cases, the word cholesterol was never mentioned. Also seldom mentioned was diabetes, which will radically alter the treatment of a heart attack victim. Poor prescriptions were also a problem with many patients leaving hospital on a low dosage of drugs.

Drugs bring enormous benefit to cardiac patients. While people are quite comfortable describing as efficacious a drug producing an absolute risk reduction of 1%, the statins in real world use bring a 2% improvement at one year, which jumps to 7% at 2 1/2 years. The reduction is even more profound with ACE inhibitors, which produce a staggering 18-20% absolute risk reduction at 2 1/2 years. These sorts of numbers are very important but they also raise some concerns. The number of drugs prescribed a heart attack victim upon discharge has risen between 1997 and today by a p value of .001, while the drop in mortality has a p-value of .56, not statistically significant. While it is possible that we simply have not followed people long enough, we should, according to clinical trial results, be seeing much more significant improvements in mortality. We have initiatives underway to try to get physicians to understand how patients take their drugs and what alternative therapies they may be taking as well in hopes of explaining this discrepancy.

We are now trying to address some of the problems and inadequacies the ICONS process has revealed. We are addressing the non-documentation of co-morbidities by implementing standardized discharge summaries so that it is impossible to send a heart attack victim home in Nova Scotia unless their cholesterol result is documented. We have been able to secure beds at tertiary care centres for heart patients from the regions. We have provided extensive education for both healthcare providers and patients. Cardiovascular disease is the largest program in the province and yet there was no coordinated approach to care. Over two years we negotiated with the Department of Health for a provincial program that would build on ICONS, and as of Spring 2002 that has been put in place. It will create a central surveillance system that will support the important disease management and academic obligations of the ICONS group. But we will also deal with developing standards, deciding what we are going to scorecard in policy and allocation issues around cardiovascular health. In the next year, we hope to develop province-wide standards for how long somebody should wait for bypass surgery and how long someone should wait to see a specialist. We hope to improve access to all our diagnostic areas and improve risk factors through efforts such as lipid management. In the treatment areas, we will address the medication burden: if 12 or more drugs are being taken by a patient, then possibly, evidence-based therapies may cease to work. Lastly, we will work to identify dangerous practices in the management of heart patients.

Dr. David Johnstone has been a Faculty member of Dalhousie University since 1978, as well as a member of the Division of Cardiology in the Department of Medicine. At present, he is a Professor of Medicine at Dalhousie University. He served as Head of the Division of Cardiology at Dalhousie University and the Chief of Cardiology at the Queen Elizabeth II Health Sciences Centre from 1990 to 2000.

Dr. Johnstone chaired the 1993 Canadian Cardiovascular Society Consensus on the Diagnosis and Management of Heart Failure. He is currently Vice President of the Canadian Cardiovascular Society. He was a Principal Investigator for the NHI Studies of Left Ventricular Dysfunction (SOLVD) Program. His general research interests include Clinical Trials and Health Service research/Outcomes studies. He is Chairman of the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) Project Steering Committee. He served as Chair of the Canadian Cardio/Cerebrovascular Research Advisory Council 2001-02.

Pharmacy practice research to optimize drug therapy
By Dr. Lisa Dolovich

Pharmacy practice research seeks to inform and understand pharmacy and the way in which it is practiced. If we look at the evolution of the practice of pharmacy over the last century, as described by Dr. Charles Hepler from the University of Florida, we see that until about 1940, pharmacists were generally manufacturers of medicines in their pharmacies. At that point pharmacists really did individualize medicines to the patients they cared for. From 1940 to 1970, the practice of pharmacy evolved to concentrate on the science of how drugs were made and how drugs exerted their actions. Pharmacy education focused on pharmaceutics, medicinal chemistry, pharmacology, and other types of science. Drug focused education resulted in pharmacists who were very knowledgeable in the scientific aspects of drug therapy but less skilled in applying their knowledge to resolve clinical problems faced by individual patients. Pharmacies and pharmacists then became more of a channel of distribution for the pharmaceutical industry as more and more drugs became pre-packaged.

Beginning around 1970, pharmacy practice moved into the era of patient care. The information age and the explosion of new drug therapies available in the marketplace meant that patients, physicians, and pharmacists faced the new challenge of evaluating multiple drug therapy choices, sifting through vast amounts of therapeutic information, and understanding how to minimize the risks when multiple drug therapies were taken together. These challenges led pharmacists to refocus their practice to clinically-oriented activities. Pharmacists began the patient care era by providing drug information, developing patient medication profiles, first manually and then by computer, and monitoring to reduce the risks of adverse drug events. Pharmacists have extended their practice over the past 30 years to become more proactive in optimizing therapeutics.

Where do pharmacists fit in?
Studies have shown that various places in the medication use process can be targeted with interventions that can optimize drug therapy. Pharmacists are well positioned to participate in these interventions. A simplistic version of the medication use system can be said to incorporate all of the steps of drug therapy. The first step is the assessment phase. In this phase, the patient develops and recognizes that they have the signs and symptoms of a medical problem. Then the patient visits their physician and the patient and physician exchange information about the signs or symptoms and treatment options available. The physician performs a complete medical assessment by gathering all of the needed information from the patient. In the second phase, decision making, the patient and physician deliberate about the therapeutic options, decide on therapy, and devise a management plan. Drug therapy is prescribed, and the patient goes to a pharmacy and has the drug therapy dispensed. In the third phase, maintenance, the patient is monitored and followed up to determine if the initial problem has been resolved and if new problems are occurring.

There are many types of intervention to optimize therapeutics including educational outreach, academic detailing, use of opinion leaders, patient focused interventions with specific recommendations and ongoing feedback to physicians. Davis et al (1995, 1999) has shown that multifaceted strategies are more successful than a single strategy and the most effective interventions are ongoing and individualized to the patient's situation. Pharmacists are well positioned to participate in many stages of this drug therapy process. Given the multifaceted nature of successful strategies, the incorporation of pharmacist-directed interventions into the medications use system should complement interventions carried out in other ways in the system.

In the last few years, Don Willison, myself and other colleagues at McMaster University have been examining potential roles for pharmacists. We have studied this topic from a theoretical perspective, using qualitative interviews, and by conducting mailed and telephone surveys to a random sample of patients, physicians, and pharmacists. This work allowed us to identify the following roles that patients, physicians and pharmacists felt were currently acceptable pharmacy practice:

- a quality assurance role, where pharmacists would examine a prescription after it has been written to ensure it met the standard of practice;
- a drug information consultant to a physician;
- a co-deliberator with a physician about drug therapy choices for a specific patient;
- a patient educator about drug therapy;
- a substitute deliberator (replacing the physician) for drug decisions if the pharmacist knows the patient;
- a consultant who performs comprehensive medication assessments at the request of the physician to assess whether the patient is taking an optimal drug regimen;
- a co-deliberator with the patient and physician if there are some complicated decisions to be made and all three parties would benefit from each other s expertise.

Our surveys found that patients and physicians preferred that pharmacists collaborated with physicians and patients and did not make drug related decisions or recommendations independent of physician consultation. The potential roles identified in our study map onto almost every part of the medication use process described earlier.

Accumulating evidence on pharmacy practice

The Canadian Pharmacists Association database of Canadian pharmacy practice research is compiling, on an ongoing basis, a list of pharmacy research studies being conducted in Canada. There are now 51 studies, conducted between 1993 and 2002, listed in the database, most of which have been carried out in community pharmacies. A Cochrane review conducted by Beney *et al* (2002) reviewed 25 studies conducted between 1966 and 1999, involving more than 40 pharmacists and 60,000 patients. When the review evaluated the effect of pharmacists versus other healthcare professionals in providing care to patients, the one study reviewed found that pharmacist care actually increased the scheduled number of healthcare services that patients used, but without producing a decrease in hospital and emergency admissions. Six studies of pharmacist intervention versus usual care (no pharmacist) found that pharmacists decreased non-scheduled health services and decreased the number of specialty physician visits. In 10 of 13 studies evaluating patients with targeted medical conditions such as asthma or heart failure, pharmacist care produced improvements in the measurements related to the targeted conditions. Pharmacists were also able to alter physician prescribing practices in 11 of 13 studies. In the four studies that measured quality of life (using the Medical Outcomes Short Form 36 [SF-36]), no change attributable to pharmacist care was found.

A number of large studies have been published that examine pharmacy practice since 1999 when the Cochrane review was done. A European study conducted by Bernten *et al* (2001) evaluated 2,500 geriatric patients in community pharmacies from seven different countries. This study found that a pharmacist providing a comprehensive assessment of medication regimens improved patient satisfaction and symptom control, but produced no difference in quality of life, hospitalizations, or processes of care. Grymonpre et al (2001) conducted a study at the University of Manitoba in a community-based healthcare clinic in geriatrics. She found that 952 issues were identified by the participating pharmacist for the 135 patients enrolled in the study. At follow-up, 29% of these issues had been partially or completely resolved. The most common issues identified related to adverse drug reactions. No differences were observed in evaluation measures such as self-reported symptoms or processes. Another study conducted by Krska *et al* (2001) of geriatrics patients in a general medicine setting found that about 40% more issues were resolved in the intervention group compared with the control group. These were drug-related issues, such as adding medication, stopping medication, and changing medication. But again, no differences were seen in the other measures such as quality of life, health services utilization or medication cost. University of Alberta researchers led by Karen Farris recently published a pharmaceutical care intervention study with geriatric patients in community pharmacies. Pharmacists in the intervention group identified a mean of 3.9 drug related problems per patient. This study also found an improvement in some elements of patient satisfaction, such as evaluation and goal-setting, and expectations that pharmacists would communicate with physicians about the patient s medication. But again, no differences in quality of life or self-reported patient adherence were found.

The Seniors Medication Assessment Research Trial (SMART) study, conducted at McMaster University by John Sellers from the Family Medicine Department, Connie Sellers, a pharmacist affiliated with the University of Toronto and others at McMaster, including myself, examined a pharmacy practice model aimed at optimizing medication use among seniors. This clustered, randomized control trial was similar in design and scope to many of the studies described above. Forty-eight physician offices participated in the study. Twenty-four expanded role pharmacists visited were partnered with the half (24) of the physician offices which were randomized to the intervention arm of the study. Each pharmacist assessed approximately 20 patients at the physician office they were paired with. The patients were all over the age of 65 and they were randomly chosen from all the rostered patients over 65 at that physician s office. The pharmacist intervention consisted of a number of components. The pharmacist conducted a medical chart review, met with the patient, completed a consultation letter, reviewed their recommendations in person with the family physician, followed up with the patient and then followed up with the family physician on the status of recommendations three months after the initial pharmacist consultation. Outcomes were measured five months after the initial pharmacist consultation with the patient.

Approximately 900 patients were included in the study, with a mean age of 74 years. The majority of patients were women, and patients were on a mean of eight different medications and 12 units of

medication per day. The pharmacists in the intervention group were able to identify 1,093 drug-related problems. Physicians intended to implement recommendations related to 837 of those 1,093 problems and physicians had actually implemented 790 of these recommendations at the three-month follow-up visit. A mean of 2.8 problems were found per patient, and 88% of patients had at least one drug-related problem. The most common problem that was found in the intervention group (this information is not available for the control group) was that patients required a drug but were not receiving it. At five months, no differences were found in the units of medication patients were taking per day, the number of medications patients were taking per day, satisfaction or quality of life. As well, no differences were found in overall costs from a health system perspective. Patient health and cost outcomes will be measured after an additional 12 months has passed (i.e. 17 months after the initial pharmacist consultation) to help determine whether the absence of effects found in this study was because the time frame of five months was too short to generate any meaningful changes in health in this population of complex elderly patients.

Other pharmacy practice studies focusing on pharmacist interventions directed at geriatric patients with a range of medical conditions have produced results similar to those described above (Volume C, 2001; Zermansky A, 2001; Granas A., 1999; Ellis S, 2000). While the group of studies already described have focused on generic interventions in geriatric patients, another set of pharmacy practice research focuses on with disease-specific interventions. The Study of Cardiovascular Intervention by Pharmacists (SCRIP) study, conducted by Tsuyuki *et al* at the University of Alberta, was a multi-centre randomized trial designed to determine the effect of a program of intervention by community pharmacists working with patients and their primary care physicians on cholesterol risk management in patients at high risk for coronary heart disease events. Patients were randomized to the pharmacist intervention or to usual care in 54 community pharmacies in Alberta and Saskatchewan. The intervention consisted of educating patients on cardiac risk factors, and encouraging them to see their primary care physician for a risk factor assessment. Measurement of the study outcomes occurred after 16 weeks. Pharmacists could conduct interim visits by telephone or in person to reinforce education, interventions, at the desired endpoints.

The SCRIP study found that the pharmacist intervention produced statistically significant results in favour of the intervention group for the combined endpoint of the performance of a cholesterol panel measurement, a new prescription of a cholesterol-lowering drug, or a dosage increase of cholesterol medication. Improvements in each of the individual components of the primary endpoint were also highly statistically significant.

Other disease-specific pharmacy practice interventions have been studied and have produced improvements for patients who received a pharmacy care intervention. Gattis *et al* (1999) found a statistically significant reduction in all-cause mortality and heart failure events in the groups who received intervention from a pharmacist who provided education about heart failure to patients and suggested alterations to their drug therapy. As well, Herborg *et al* (2001) found that pharmacists' interventions increased the use of inhaled cortical steroids and decreased the use of beta-agonists in patients with asthma (although it is important to note that while this study had a control group, it was not randomized like the other studies described above).

These various studies tell us that patients have unresolved drug-related problems that pharmacists are able to identify. Pharmacists can make recommendations that physicians agree with and implement. However, the effects of pharmacist intervention on patients' clinical outcomes are mixed. The lack of substantial effect on clinical outcomes may be because the large changes in clinical outcomes are difficult to attain in the complex geriatric patient populations involved in these studies, or it could be that the measurement instruments used are not responsive to change. It also seems that disease specific studies are better able to demonstrate clinically meaningful changes for patients compared with studies using a generic pharmacist intervention applied across disease states.

The impact of pharmacy practice research on policy

It is useful to examine a framework of knowledge utilization to better understand the impact of pharmacy practice research on policy. The six stages of knowledge utilization proposed by Knott and Wildavsky, and modified by Landry (1999) are the following: transmission, cognition, reference, effort, influence, and application. Examples of how pharmacy practice research has instigated policy initiatives fall into three categories: standards and policy statements, legislation, and reimbursement for pharmacists to provide clinical services.

In 2000, the Ontario College of Pharmacists reissued their standards of practice. The first standard was enhanced to state: The pharmacist, using unique knowledge and skills to meet a patient's drug-related needs, practices patient-focused care in partnership with patients and other health care providers to

achieve positive health outcomes and/or maintain or improve quality of life for the patient. This standard has been operationalized so that pharmacists are now expected to ensure that appropriate patient information is gathered and recorded to establish a profile that permits patient-focused care. Pharmacists are expected to evaluate the patient s drug therapy when information is available, and if potential or actual drug-related problems are identified, the pharmacist is expected to determine appropriate therapeutic options to solve or prevent them. These are now the operational standards to which pharmacists are held minimally accountable across the country.

Another example of recent policy is the 1996 joint policy statement of the Canadian Medical Association (CMA) and the Canadian Pharmacists Association (CPA), entitled Approaches to Enhancing the Quality of Drug Therapy. This policy statement makes explicit references to the benefit of collaboration between physicians to optimize drug therapy. In 2002, the American College of Physicians and the American Society of Internal Medicine released a statement on the pharmacists' scope of practice that outlines how the medical and pharmacy professions can work together to enhance patient safety and quality of care.

Legislation was introduced in 2001 to the United States Congress to amend the Social Security Act and place pharmacists on the list of health care professionals classified as health care providers. This legislation, if passed, would enable pharmacists to bill for high-level patient care services provided to Medicare beneficiaries. Although it was set aside in the wake of the September 11 tragedy, similar legislation is now being considered.

Finally, reimbursement policy determines how we compensate pharmacists for their clinical services. Quebec allows pharmacists to bill the provincial drug plan for providing a pharmaceutical opinion on improving drug therapy or for a refusal to fill a prescription. The Canadian Forces programs of the Department of National Defense also recently adopted that program for the members of the Canadian Armed Forces, adjudicated through Atlantic Blue Cross. The Canadian Forces has also implemented a program to provide over-the-counter (OTC) drugs to Canadian Forces members for free if they undergo an assessment for the OTC medication by a pharmacist. There are a number of third-party pilot projects across Canada that will reimburse pharmacists for activities such as trial prescriptions or cognitive services. There are also efforts underway to integrate pharmacists as clinical care providers in primary care networks.

These examples of policy show how pharmacy practice research has been cited in the justification for policy statements (the reference stage of knowledge utilization), has been used to generate standards of practice for pharmacists (the effort stage of knowledge utilization) and has been used to create legislation and reimbursement programs related to patient-centred pharmacy practice (the application stage of knowledge utilization). Future issues that may result in new programs or policies related to prescribing by pharmacists and pharmacist reimbursement for follow-up of new prescriptions to help prevent drug-related morbidity and mortality.

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Dr. Dolovich conducts research in the areas of pharmacy and physician practice, health care systems, patients view about medications, and therapeutics. Dr. Dolovich leads the Team for Individualizing Pharmacotherapy in Primary Care for Seniors (TIPPS). In 2001 Dr. Dolovich was recognized with the Piafsky Young Investigator Award by Canadian Society of Clinical Pharmacology and as the Preceptor of the Year by the Doctor of Pharmacy Program at the University of Toronto.

The impact of new drugs on health and economic growth: The econometric evidence
By Dr. Frank Lichtenberg

For the past eight years, I have been studying the contribution of new drugs to health and economic growth in the US. My key finding is that the aggregate benefit to society of new drugs exceeds their costs. That may sound obvious to some people, but others find the statement very controversial. I do not study particular drugs or even particular diseases, but rather the aggregate effects of drug innovation in general. I try to identify three types of benefits. The pocketbook effect is the effect on overall medical expenditures, and there is strong evidence that the use of new drugs actually decreases overall medical expenditures. New drugs also reduce limitations on work and other activities, and they increase longevity. Therefore, policies that reduce the number and availability of new drugs may deprive society of these benefits and ought to be considered very carefully. Policies affect both the incentives to develop new drugs and the probability that they will be used.

Economists believe that product innovation is extremely important. Grossman & Hellman published a book about 10 years ago in which they argued that innovative goods are better than older products simply because they provide more product services in relation to their cost of production. That is, new goods cost more than old goods but the quality difference is more than worth the price difference. Similarly, Bresnihan and Gordon published a book in which they argued that new goods are at the heart of economic progress. If we want to understand why people are economically better off today then they were 50 or 100 years ago, the main reason is new goods. Not just a greater quantity of goods, but better quality goods. The pharmaceutical industry is one of the most research and development (R&D) intensive industries in the economy. It has a greater propensity to generate new goods than almost any other industry. R&D expenditure as a percentage of sales in pharmaceuticals is over 10%, compared to 3% for the average industry. Even the computer industry spends much less on R&D than the pharmaceutical industry.

The key hypothesis I try to examine in my research is that, all other things being equal, a person's health is an increasing function of the vintage of the drugs he or she consumes. I hypothesize in general that new drugs are of higher quality than old drugs in the same therapeutic class. I try to investigate that hypothesis in a variety of ways. These studies are all based on large, comprehensive government databases, many of which contain several decades of information on drug utilization, mortality, and medical costs for the US population. I study this at several different levels of aggregation: at the patient level, at the condition level, and at the national level.

I look at the dollars saved, in terms of overall medical expenditure for a patient, by replacing old drugs with new drugs for given diseases. I control for potentially confounding factors that could be correlated with the age of the drug, such as the age of the patient, sex, race, education, income, diagnosis, insurance status, disease duration, and number of co-morbidities. To illustrate the methodology, suppose we observe two 70-year old white high school graduates. Both have an income of $40,000, and are covered by Medicare and private insurance. They are both taking an anti-arrhythmic medication for a condition they have had for 12 years. This is the extent to which I can standardize with these databases. One of these people is taking a drug approved by the FDA in 1950 and the other is taking a drug approved in 1995. I want to compare the outcomes and expenditure of these two individuals, controlling for all the other factors.

Essentially, what I find is that newer drugs are associated with lower total medical costs and fewer lost work-days. In fact, the reduction in medical expenditures from using a newer drug is almost four times greater than the added cost of the new drug. That means that if we replace a prescription for a 15-year old drug with one for a five-year old drug, drug expenditure would increase by $18. But the switch to the newer drug reduces the use and cost of medical services including hospital stays, office visits, home healthcare, and outpatient visits. The estimated reduction in non-drug medical costs is $71 compared to the $18 increase in drug cost. Much of that savings comes from reduced hospital care. Switching from the old drug to the new drug reduces expected hospital admissions by about 6 per 1,000 people or .006. This sounds like a small number but the average cost of a hospital admission is $8,000, and that multiplied by .006 is $48, which is more than the $18 additional cost of the new drug. Most of the savings I found in that study came from a reduced number of hospital admissions, but there were additional savings from reduced length of stay.

I have updated that study using more recent data, which has enabled me to expand the sample up through 1998. The new estimates suggest that the savings may be even larger. They indicate that use of the newer drug -- which costs $18 more -- reduces other medical costs by about $130, on average. The reduction in medical costs incurred by just one payer, Medicare, exceeds the increase in drug costs. An increase in drug expense associated with the newer

drug of $18 brings a reduction in hospital expense of about $80, as well as reductions in office visits and in home healthcare, etc. The savings appear to be quite substantial.

The second type of benefit is the reduction in limitations on work and other activities, also known as quality of life or employee productivity. When we talk about economic prosperity, the most commonly used measure is output per person. Output per person depends on several factors, not only output per hour worked but also hours worked per employed person and the employment rate the probability that someone in the working age population can be employed. I hypothesize that new drugs will affect all three of these variables. In particular, new drugs may enable people who would otherwise be chronically ill to work, and may result in reduced work loss days. This is no small problem in the US: 8% of people aged 45 to 54 say they are unable to work due to illness or disability. About eight or nine million people aged 18-65 say that they are unable to work due to illness or disability. New drugs become very valuable to the extent that they enable this population to become productive.

The impact of new drugs on mortality: the case of HIV and orphan diseases

The third major area in which I have tried to study the impact of new drug utilization is longevity. I have completed two case studies, one in HIV and the other in orphan drugs, where there were large, sudden increases in the number of drugs on the market. I have also studied this issue in a more comprehensive way using data for all diseases. 1987 was the first year in which the Centers for Disease Control listed HIV as a cause of death. There was a very dramatic, steady increase in HIV mortality up until 1995, followed by an equally dramatic reversal. My hypothesis was that the development, FDA approval, and use of new HIV drugs played an important role in this dramatic reduction in mortality, and I looked at aggregate data to support it. The US FDA keeps very precise information about every drug on the market for a given disease, making it possible to identify all the drugs approved with HIV as an indication. Aside from a few very old drugs that are currently used for the treatment of HIV, most the HIV drugs currently in use started to come on line in the late 1980s, with a real acceleration starting in 1995. Between 1987 and 1993 only four HIV drugs were approved, at a rate of 0.6 drugs per year. But in the following five years there were 10 HIV drugs approved, or two drugs a year.

The trend in the introduction of new drugs over these years closely mirrors the trend in mortality, with a very similar turning point. Based on regression of the relationship between the number of HIV drug approvals and the reduction in HIV mortality, I estimate that the annual number of HIV deaths is reduced by about 6,000 per year for each additional HIV drug approval. This confirms other more micro evidence about the role of new drug approvals in the decline in HIV mortality.

The other case study involved the Orphan Drug Act. US Congress passed this Act in 1983 to promote the development of products that demonstrate promise for the diagnosis and/or treatment of a rare disease or condition, which was later defined as one that affects fewer than 200,000 Americans. The market responded strongly to the Act: in the decade before its introduction, there was only one drug for orphan diseases approved per year. But in the 15 years after the Act there were 12 new drugs per year, which represents a twelve-fold increase in the rate of innovation. I wanted to see what effect this had on health outcomes. I measured mortality from rare diseases using standard mortality data, and contrasted that with mortality from common diseases. In this analysis, I defined a rare disease as an ICD-9 disease that caused less than 5,000 deaths per year. In the decade prior to the Orphan Drug Act, that is, between 1970 and 1980, mortality from rare diseases increased at roughly the same rate as mortality from common diseases. But if we continue the comparison well beyond the Act's institution, to 1995, we actually see a sharp decline in mortality from rare diseases while mortality from common diseases continued to increase. The relative risk of dying from a rare disease fell dramatically, and that was presumably in response to the availability of orphan drugs as they came down the pipeline. One lesson to derive from the Orphan Drug Act is that creating incentives for innovation does in fact matter. It affects the amount of innovation, which, in turn, affects health and economic wellbeing.

The impact of new drugs on longevity

The next study was more comprehensive, asking in very general terms whether new drug approvals have a real and important effect on mortality in general. I first looked at data on longevity for all diseases over the period 1979 to 1998. The mean age at death increased by about three or four years. So people were dying four years older in 1998 than they were in 1979. But longevity gains vary quite a bit across diseases. There are a few remarkable cases in which mean age of death actually went up by 18 years over that period. And there are a few diseases where mean age of death actually declined. I wanted to know what explained the variation across diseases. A data source called the National Drug Data File allowed me to identify all of the drugs indicated for treatment of

different conditions, whether tuberculosis or hypercholesterolemia. I included some unlabeled indications, following the American Medical Association's Council on Scientific Affairs statement that unlabeled uses are very important, that the prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial, and that prescribing drugs for unlabeled uses is often necessary for optimal patient care.

There is considerable variation across diseases in the extent and timing of increases in the stock of available drugs. For example, disorders of the thyroid gland and disorders of other endocrine gland are right next to each other in the disease classification. But when we look at the number of drugs available to treat each condition in each year as a percent of the number of drugs available to treat that condition in the initial year of 1979, we see some important differences. Between 1979 and 1984, the number of drugs available to treat thyroid disorders increased by about 30%, after which it remained constant: there were no new drugs for treating thyroid disorders after 1984. Drugs to treat endocrine disorders were slower off the mark, but ultimately there was a 50% increase over this period in the number of drugs available to treat endocrine disorders. By exploiting this variation in the rate of increase in the number of drugs available to treat different diseases, we can examine whether these rates are related to changes in mortality at the disease level.

I distinguished in this analysis between priority review and standard review drugs as defined by the FDA. Priority review drugs are those that in the opinion of the FDA represent a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. Standard review drugs are "me too" drugs according to the FDA. So one hypothesis is that, if the FDA is getting it right, standard review drugs are not really going to increase longevity while priority review drugs will.

If we look at two diseases: ICD code 09 (syphilis and other venereal diseases) and ICD code 20 (malignant neoplasm of lymphatic and hematopoietic tissue), we see that 16 new drugs were approved to treat syphilis, only five of which were priority drugs, whereas 14 drugs were approved to treat lymph cancer, of which 10 were priority drugs. In the econometric model I used, the dependent variable is mean age at death: the mean age at which deaths caused by a particular disease in a particular year occur. For example, what was the mean age of people who died of heart attacks in 1988? We can measure that average for various diseases annually over a 20-year period, then look at it as a function of the number of drugs approved to treat that disease up until that year. For each disease I can track the increase in the number of drugs and also distinguish between priority review and standard review drugs. This approach controls for the effect of changes in aggregate determinants of mortality.

What I found was strong support for the hypothesis that mean age of death is in fact positively related to the number of drugs available to treat a disease. As the number of drugs available goes up, mean age of death goes up. However, I found that only priority review drug approvals increase mean age of death, and that this relationship is incredibly strong, with a p value of 1 in 10,000. We can therefore easily reject the hypothesis that the accumulation of the stock of drugs does not matter.

Mean age of death increased by 3.8 years from 1979 to 1998. I estimated that the increase in the stock of priority review drugs increased mean age of death by about 0.4 years, or 4.7 months. (This estimate is likely to be conservative.) That is, we can all expect to live 4.7 months longer due to 20 years of pharmaceutical innovation. We can then measure the cost versus the longevity benefits of new drug approvals. During the period 1979-1998, there were about 500 new molecular entities, or 25 new drugs per year, approved by the FDA. An Office of Technology Assessment study indicated that the average cost of a new drug approval is about US $360 million during that period. If there were about 500 new drugs and each one of them cost $360 million to develop, the total cost of all of the drug development was about US $182 billion dollars. To measure and value the longevity benefits, we first calculated the total number of life years gained per year as about 800,000 life years as an annual gain. A number of authors have estimated that the value of a life year is approximately US $150,000. We may question how people come up with those estimates, but I will use that here as an extraneous estimate of what the value of a life-year might be. If we use that number, then the value of the annual gain in life years is about US $120 billion (800,000 life years each valued at $150,000).That figure can be viewed as an annuity which we receive every year: once these drugs are on the market, they provide a perpetual longevity benefit.

The rate of return on new drug development

It has been estimated that in the last two decades, drug development usually takes about 14 years and is actually rising. I estimated that the total cost of drug development was about US $182 billion, which we can spread out over a 14-year period. In other words, during years 1 through 14 we were spending about $13 billion a year on drug development without enjoying the benefits. In year 15, and in all

subsequent years, the population experiences a gain in life years that has an annual value of $120 billion. The internal rate of return to this series of cash flows is 18, and it turns out to be quite sensitive to the length of the drug development cycle. This rate of return reflects only the value of increased longevity among Americans. It does not count Canadian longevity in the calculation, for example, and it also does not count the other benefits of new drugs, including reduced hospital expenditure and reduced limitations on work and other activities.

In some very recent research, I have applied the same kind of methodology to productivity variables: What percent of people with a condition are unable to work? The national health interview survey asks 60,000 or so people a year how healthy they are. What health conditions do they have; arthritis, diabetes, etc. If you have arthritis, are you unable to work because of it? How many days of work did you miss because of your arthritis? Now, we can measure this over time.

In this study I looked at the effect of the number of drugs available to treat a condition on the probability of being unable to work due to that condition and on the number of workdays lost due to the condition. Similar to the previous results, if we look at 1983 and calculate the average number of drugs available to treat a condition, weighted by its relative prevalence, we find that the average condition was treatable by 24 drugs. By 1996, that average had increased by about 50%, but it varied a lot across medical conditions. The increase in the number of drugs on the market between 1983 and 1996 reduced all of the following variables by about 12% in 1996: the number of people unable to work; work-loss days of currently employed persons; restricted activity days and bed days of all persons.

I found a negative and significant correlation across diseases between the increase in the number of drugs available and the decrease in the probability of being unable to work. New drug approvals that occurred between 1983 and 1996 reduced the number of people unable to work by about 1.4 million people. This means that in 1996, there were about 1.4 million more people able to work than would have been working if there had been no new drugs in the previous 14 years. If we value a year of work at the average wage of American workers, which is about US $30,000 per year, the value of the reduction in the number of people unable to work is about US $43 billion per year. There is also a reduction in work loss days per year of people who are employed. The dollar value of that, with a savings of about 100 million work days per year valued at about US $100 per day, is about US $10 billion per year. New drugs approved between 1983 and 1996 also reduced the aggregate number of restricted activity days by about 400 million days.

My past research has identified the benefits of new drugs to Americans. I am now beginning to study the global health and economic effects of the international diffusion of new drugs. Improvements in health constitute an important part of economic progress. Medical innovation in general, and new drugs in particular, has contributed importantly to health, and will continue to do so in the future.

Dr. Frank Lichtenberg is Courtney C. Brown Professor of Business at Columbia University. Dr. Lichtenberg has also taught at Harvard University, and served as an econometrics expert for the Federal Trade Commission. His research focuses on the introduction of new technologies arising from R&D and how those new technologies affect productivity of companies, industries and political jurisdictions.

The Pharmaceutical Industry and Public Policy in the Post Genomics Era
By Dr. Mark Poznansky

Public policy affects both our capacity to produce innovative drug therapies and our ability to use them. Perhaps nowhere is public policy more important than in our health care system and in the associated industries. Public policy pervades our universities, our hospitals, our research and innovation agenda, our introduction of new drugs and medical procedures and our intellectual and industrial competitiveness with the rest of the world. If we are to succeed in maintaining the high standard of living that Canadians enjoy then we must be able to compete. Strong and effective public policy is at the center of this challenge.

Creating an innovative nation

Amongst the major economic problems we have in Canada is the very significant dependence on our natural resources and the fact that commodity prices have being going down steadily over the past 200 years. If we continue to be dependent on water, wheat, oil and other natural resources, our wealth and prosperity will continue to head downwards. To quote Roger Martin, Dean of the Rotman School of Management, The argument is as simple as it is compelling: innovation drives competitiveness and competitiveness drives prosperity. Canada's prosperity is falling. From 1990 to 2000, we dropped from 3rd to 8th place, behind such countries as Denmark, Norway, and Ireland. There is very strong evidence that the rise of countries like the three I just named can be directly attributed to their very strong policies supporting innovation.

On the positive side, some of our leaders now appear to be taking the innovation agenda seriously. Prime Minister Chretien has talked about Canada becoming one of the top five countries in the world in terms of research; Ontario Premier Harris spoke of becoming one of the top three jurisdictions in North America for the biopharmaceutical industries. These are huge objectives that will require massive commitments, especially on the financial end and in the support of university-based research. A study by the National Science Foundation showed that between 1988 and 1998, 75% of all citations in drugs and medical innovations that were commercialized came from government-supported university laboratories.

However good Canadian universities are at creating knowledge, they do not know how to capture it. We have too many examples of Canadian innovations being commercialized for the benefit of partners from south of the border. If we look at the number of patents filed on university research, the difference between the US and Canada becomes quite stark. In 1999, the number of patents filed from Stanford and the Massachussetts Institute of Technology (MIT) are similar, while the University of Toronto, which is actually larger than either Stanford or MIT, and has outstanding research based on publications, filed only one fifth to one quarter as many patents. The number of patents issued is even worse, the number license-executed with equity is horrendous, and the number of start-up companies is very low. The University of Toronto is typical of Canadian universities. Obviously, the process of translating innovation into commercialization is being done very poorly.

We also lag behind in government support for research. In 2002, federal government investment per capita in medical research in the US is seven times higher than in Canada, not all of which can be attributed to the weak Canadian dollar. Venture capital investments in biotechnology are 10 times higher in Massachusetts than in Ontario. Although the specific data is not available, it is likely that Canadians invest more money in American biotechnology companies than they do in Canadian ones.

Grading Public Policy

I have prepared my own personal report card on public policy. I have assigned grades in three areas: innovation, regulation, and public understanding, and included some consideration for effort as well as results. In 1995, our governments all got Fs in innovation; they simply did not think it was important as they felt our prosperity would continue to be generated by natural resources. Between 1995 and 2002, we began to develop very high aspirations about innovation, through Paul Martin federally, Ernie Eaves in Ontario, and the performance of the Quebec government. The grade for innovation is now up to a B-, reflecting the establishment of the Canada Foundation for Innovation and the Canadian Institutes of Health Research, and Ontario initiatives like the Ontario Research and Development Challenge Fund, the Ontario Innovation Trust and the MARS project. The amount of money being poured into science from all levels of government, as well as investment from the private sector, is outstanding. I have given similar grades with respect to regulation.

In terms of public understanding, Canadians are reading more science in the newspapers and hearing about it more in other media. But we have not yet made the breakthrough in the public appeal of science where it has become a major industry . The data comparing California and Ontario is overwhelming. While there are only twice as many life

science graduates in California as there are in Ontario, there are seven times more companies, and, most importantly, 21 times more revenue generated by companies in California than in Ontario. California has 31 times more R&D expenditures, which is a very important predictor of innovation. And finally, the number of employees paying high taxes is 40 times higher in California than in Ontario.

Building on our strengths

We do have some building blocks to work with. Our medical research and there are good metrics to measure the quality of medical research is really outstanding. The first single-disease genes for cystic fibrosis and muscular dystrophy were found at Toronto s Hospital for Sick Children (though they were commercialized in the US). Our public healthcare system lends itself to outstanding clinical research, because we basically have some of the world's largest health maintenance organizations (HMO)s. In recent years, we have had very responsive governments, not only federally but provincially. As well, it is important to remember that the post-genomic era is in the early innings, and we still have time to become competitive.

The first steps are public investment for R&D. Governments have started to do this in a very important way but we are still way behind the US. While some politicians blame this largely on the private sector, I would argue that the private sector is not investing enough in Canada simply because there is not yet enough to invest in. We do, however, have serious problems on the building businesses side. Venture capital in Canada is not yet onside to the realities of Biotech. We have a difficult regulatory environment. We have difficulty attracting entrepreneurs and managers in this sector. Most importantly, we might ask whether we have a deep philosophical problem as a country: if Canada really is a risk-averse society, as we sometimes appear to be, then no amount of effort will make us innovative.

Some say that Canada s small market size makes it difficult for us to stand up and be noticed. But what others do notice about us are the impediments we erect to attracting investment and encouraging innovation. The dark cloud over Canada is our regulatory and patent protection environment, which is a major concern for business leaders and investors. Many people may think that I am overstating the problem: our patent environment is not that bad, though there are some problems with patent restoration, and our regulations are not that bad. But the point is that if the major players have this perception of us then we have a problem. We need to change the ideas held by major investment houses in New York that we are a slow, cold, poor investment with lousy regulation and no patent protection

Public policy challenges of the post-genomics era

Technology changes quickly while policies and governments change very slowly. Technology often leapfrogs policy, as it has with the Royal Commission on Reproductive Technologies. The legislation has not yet been passed and already there is a slew of new technologies not even touched on by the Commission. Today s technology cannot be dealt with at that slow pace, and the rates of change are growing ever faster in the post-genomic era.

Between the years 1800 and 2001, most of our drugs were really based on poisons. Poisons that came from the earth, from plants, from other animals, and we tried to figure out if we could find a dose of that poison that would allow us to rectify a clinical condition without disturbing other physiological processes. Starting somewhere around 1995, but really coming strong now, is the advent of drugs based on natural and often human biological processes. This is the result of advances in genomics, the establishment of proteomics and a real understanding of cell biology. A key to these developments has been the area of high-speed computation, which allows us to develop many of these natural-based drugs. In the last 60 years, we developed about 500 drug targets. In the next 10 years, we are going to develop between 5,000 and 10,000 new drug targets as a result of our understanding of the human genome and the relationship between genes and biological processes.

In the 1980s and 1990s, a disease gene took five years and about $2.5 million to identify; by 2001 a disease gene could be had with about $100,000 and two months work. Today, if you know where you are looking for a disease gene, you can identify it in a couple of hours at a cost of $150. That is the rate of change we have to deal with. About four years ago, the Robarts Research Institute awarded its annual prize, the Taylor International, to the innovative work of Michael Gibrone from Harvard. Traditionally, if you are looking to see whether a given biological process affects a gene, you isolate the biological process and look at the expression of one gene, which can take about a week. Michael Gibrone used a microchip technology at MIT to do the same experiment, and rather than looking at the biological effect and biological process on one gene, he was able to look at 10,000 genes at the same time, in one day. These technologies are now available routinely in many laboratories in North America, including here in Canada.

Tailoring and targeting drug therapy

Pharmaco-genomics is a very important concept,

which will have a major effect on healthcare over the next couple of years. I will use as an example the drug used to treat irritable bowel syndrome, cisiprid. Until last year, three million doses of this drug were used each day for irritable bowel syndrome, mostly in North American women. It is an incredibly effective drug. Unfortunately, about four or five years ago, doctors started to see heart problems in a very small number of patients who took the drug. After a couple of deaths, the drug was taken off the market, but that means millions of North Americans are denied access to a drug because a few hundred experienced adverse drug reactions. Within the next few years, we will be able to identify those individuals ahead of time through genotyping and put drugs like that back on the market, confident that we can avoid giving it to individuals who are genetically pre-disposed to the arrhythmia has been found to produce.

Today s medicine is largely population-based, but tomorrow s medicine will be individualized. We will know exactly who will respond to which ACE inhibitor or which statin. And all our processes are going to have to adapt to that reality. There will be hiccups on the road to our being able to use genomics effectively in healthcare, but we ought not to get too excited about those hiccups. "Dolly the cloned sheep's arthritis raises concerns over cloning," represents the kind of thing we need to expect. We need to take them seriously, but not as reasons to stop moving ahead. Think of transplantation. Before we had cyclosporine, all transplant patients died and they had pretty lousy lives in the years between their transplants and their deaths. But as the problem became clear, we developed new and better immunosuppressive agents, which now allow people to live healthy, productive lives with their transplants. We can expect the same with genetic manipulations. The fact that Dolly developed arthritis is not so nice for Dolly, and it shows the biotech industry that they still have work to do, but it does not negate the value of the scientific advance.

The process of pharmaco-genomics is already bringing safer and more effective drugs. But these drugs will be discovered and developed so quickly that I do not think we are going to see classes of drugs like ACE inhibitors and statins that remain common therapy for 20 or 30 years. I believe that the rate of discovery of new drugs is going to be so fast that the shelf-life of those drugs will drop to 15, 10 and maybe even fewer years. There will be more drugs for specific populations. Clinical trials will have to be shorter, smaller and cheaper. All for the same reasons: if we are going to have a drug on the market for just five or six years, we are not going to be able to spend so much money on clinical trials. We will have to develop much better surrogate endpoints for drugs, and we can expect fewer endpoint trials that involve morbidity and mortality. The Robarts Research Institute and other institutes are working to develop that type of early surrogacy using imaging technologies. The pace of discovery and implementation will be astounding and the pressure on public policy will be intense. If we think that scientists, the public, and the pharmaceutical industry are putting pressure on our regulatory systems today, just wait until tomorrow.

Dr. Mark Poznansky s scientific career brought him from McGill University to Harvard to Paris and then to Edmonton, where he was Associate Dean of Medicine in charge of research at the University of Alberta . He is author of some 75 full publications and his laboratory generated three international patents in the area of immobilized enzymes. His tenure at the University of Alberta also coincided with the construction of two major research facilities. He became President and Scientific Director of the John P. Robarts Research Institute in 1993, succeeding the Institute s founding president, Dr. Henry Barnett. Since his arrival, the Institute has undergone impressive growth, has seen an aggressive technology transfer process put in place, and seven companies spun out of the Institute. Dr. Poznansky is founder and current president of London Biotechnology Incubator Inc., and chairs the scientific advisory board of the Canadian Medical Discoveries Fund.

Using evidence in the real world: Perspectives from a health economist, a physician, a patient, and a policy maker

How is pharmaco-economic evidence used?
By Jean-Pierre Gregoire

Over the last 10 years interest in economic evidence on drugs has increased and many jurisdictions now request economic information from drug manufacturers. The UK demands it not only from drug manufacturers but also from health technology manufacturers. In Canada, Ontario requests this information and most of the other provinces encourage manufacturers to provide it. This increased interest raises a number of questions about the methodology employed in economic evaluations.

The first issue is evidence. Evidence of effectiveness in regular clinical use is limited at the time new technologies and drugs are launched. The evidence is based on a number of assumptions and working models used to extrapolate the benefits of the technology long-term. The shortfalls of this method are leading to discussion today about instituting a two-stage assessment of economic evidence, one at the time of launch and the second a few years later when real-world effectiveness evidence is available.

Second is harmonization. While the guidelines and methodology used in economic evaluation are quite harmonized, the policies they produce are not. In fact, very little is known about the use of economic evaluation in health care decision-making. Three surveys conducted in Europe were reported by Michael Drummond in 2001 in the *European Journal of Health Economics*. Decision-makers were asked about their knowledge of economic evaluation methods, the actual and potential use of study results, and the barriers and incentives to the increased use of economic evidence. What we learned from these surveys is that the use of economic evidence is very limited.

While we still do not know how economic evaluations are used, we do know that the same evidence will produce very different decisions about drug listings from one jurisdiction to the next. In a study published last year in the *Canadian Journal of Public Health*, my colleagues and I identified 148 new chemical entities that received notice of compliance in Canada between 1992 and 1998. We then assessed their listing status in each province by January 1999: what proportion in each of the provinces were listed with no restriction, listed with restrictions, and not listed at all. Significant variations appeared between provinces. There was a very high proportion of new drugs listed in Quebec, followed by BC, where more than half had restricted status. The provinces listing the fewest new drugs were PEI, Newfoundland, and Ontario. We recognized that some of those drugs were being made accessible through special programs administered by hospitals, but the variations persisted in drugs where this was not the case. Finally, we assessed the agreement between the different provincial formularies regarding particular drugs. A Kappa statistic of .75 reflects excellent agreement and we do not see that anywhere. The highest concurrence was between Alberta and Nova Scotia, at .6, but most of the agreement was only fair, around .4, or even poor, below .4.

Among the provinces that list the most new drugs, namely Quebec and BC, agreement is poor at .34. Among provinces that list the least, PEI and Newfoundland, agreement is very poor as well. So the listing status of a particular drug is not related to the proportion of drugs listed. Researchers from the University of British Columbia published a study last year on the same topic and, using a somewhat different methodology, reached similar conclusions about the variability of formulary listings. If we assume that the same clinical and economic evidence is available to decision makers in each province, we can conclude that this evidence is not used the same way by everybody.

Dr. Jean-Pierre Gregoire is Director of Health Economics at Merck Frosst Canada Inc.

How do doctors use evidence?
By Dr. Paul Oh

Here is my world: I am a doctor, I read a paper or abstract and conclude that this new drug or technology is a good thing that I will give to my patient. Doctors base their decisions on a number of different considerations, including efficacy, safety and perhaps what the practice guidelines say. Cost is not one of these considerations. Indeed, many doctors believe that if they thought about costs they would make some bad decisions.

And not surprisingly, expenditures on medications are rising, which, according to Dr. Lichtenberg and Dr. Poznansky, may be a good thing. There are a lot of new drugs available, a lot of new indications for existing drugs and, as our population ages, more people who can benefit from these drugs. Maybe they should not be filtered because if I prescribe them people will live longer and be healthier, even if they are more expensive. Then I see Jack Nicholson on CNN saying, "I'm on this great new drug and you should be too." That puts a whole other set of considerations before the doctor who is trying to make sound prescribing decisions.

Doctors learn how to prescribe mainly from their teachers and colleagues. Sometimes they read journals; often they carry little handbooks. The ongoing major challenge is to critically appraise and filter these sources of information. We cannot assume that just because it is in print, it is valuable or even accurate. There is very little exposure to pharmacology in medical school and very few academic representatives visiting these busy doctors. The evidence for all these new product areas is variable, making it difficult to say with assurance that this chemical entity is better or safer than that one. The question we always have to ask is why is this better than what I am using? There is always some little quirk that is dwelt on in advertising, and doctors need to filter that information to make sure it makes a difference to patient outcome.

We have an overabundance of literature. More papers, more journals, more e-news than ever before. It is a challenge to find the time to sift through all this information, let alone get to the next level of critical appraisal. On the positive side, corporations and core curriculums in medical training are paying more attention to developing the skills for critical appraisal, but this is at a very early stage. Doctors are very good at talking p value without really understanding what it is and what importance it has to our patients. Does yet another study with a marginal p value represent a real advance for my patient? Time and education are needed, but in today s world, most doctors do not have the time to read and consider a journal that takes half a day to digest. The overview and summaries of the wealth of information may be helpful but these also need to be appraised.

The informed patient

The patient s voice has also become louder, with many patients bringing their own research and critical appraisals to their doctor visits. That can be helpful in patient encounters, but also presents a challenge, because individual investigations lead to misperceptions as often as they lead to understanding. For example, one patient who had seen blood in his urine was concerned after reading that a particular statin could cause liver problems. He told me that he had stopped his cholesterol lowering therapy as a result, exposing him instead to some risk of myocardial infarction. The next clinical visit was spent discussing the fact that the liver and the kidney (the source of blood in the urine) are in fact separate organs. That was certainly a valuable education session but it illustrated painfully how a single line in a newspaper clipping could undo years of careful clinical trial research. Increasing awareness may be helpful, but we need to question the balance of the portrayal of risks and benefits and the necessary background to appreciate these concepts in the general media.

Keeping up to date

Guidelines have become an industry for many academic organizations. They are certainly useful but present similar challenges in identifying sources, filtering and synthesizing. For example, there are at least 20 published guidelines on antibiotics and I will likely spend more time deciding which one to read than on their actual content. For guidelines to be useful, I need them to be simple, I need them to be in a user-friendly format, I want them to help me with my patients and not be a barrier to care.

Continuing medical education is a definite challenge, and I think we are seeing some advances in this area. There is greater advanced accreditation of educational sessions, which forces us to go through that filtering process a priori by establishing learning objectives and evaluating criteria and thus improving the quality of information presented. For the physician, the challenge every day is selection. I could choose to spend an hour here or elsewhere in a more exotic location, and there are different forces that enter into my decision. At the Royal College level, maintenance of competency and certification are tied together with completion of a breadth of educational activities. That is a positive force: we should be accountable for our knowledge, and forced to keep up to date. What doctors need as the rate of

change steps up is to keep that open, critical mind and not just accept whatever is presented to us.

Dr. Paul Oh obtained his M.D. from the University of Toronto in 1988 where he is now a lecturer. He is also staff physician in the Department of Medicine at Sunnybrook Health Science Centre in the Divisions of Clinical Pharmacology, General Internal Medicine, Cardiology and Epidemiology. Dr. Oh is the Medical Director of the B4 Medical Unit and Executive Director of the Health Outcomes and Pharmacoeconomics Research Centre at Sunnybrook. He has been a reviewer for the Drug Programs Branch since 1997 and a member of the DQTC since 1999.

Patients and evidence
By Lisa Crawford

The Arthritis Society is anomolous in that it has a patient advocacy group under its umbrella. The Canadian Arthritis Patients Alliance (CAPA) creates links between Canadians with arthritis, assists them to become more effective advocates, and seeks to improve quality of life for all people living with arthritis. We believe that it is the consumer and patient who is going to change the face of arthritis in this country, not institutions like the Arthritis Society nor professional organizations. Consumers should be involved in decision-making about drugs, and I will present two models of consumer involvement, describe the benefits and challenges evidence presents to the consumer, and outline what optimal drug policy would look like from the consumer perspective.

What is most important to patients is timely access to the best evidence-based medicines through a safe and efficient drug review system. At the federal level this means having efficient approvals of medications, and at the provincial level this means assuring universal access. The second priority is post-market surveillance: having an effective monitoring of drugs once they are in the marketplace. The third priority is public participation in the decision making process around drugs and decision-maker accountability to the public. Consumers are the end-users of drug policy and they need to be engaged throughout the process.

People are only just beginning to recognize the need to have consumers at the table when it comes to health policy in general and drug policy in particular. There is evidence showing that consumer involvement is essential to asking meaningful questions, designing good research protocols, and monitoring research progress. The arthritis arena is quite advanced in terms of having consumers participate in the evaluation of research proposals.

How does the consumer benefit from evidence?

Evidence empowers the consumer to make better decisions throughout their use of drug therapy. It puts the consumer on a more level playing field with the health care team and it increases consumer confidence in themselves, their health care team, and the health care system. One good model of consumer involvement in evidence is the Cochrane International Collaboration, which is very good at involving the consumer in synthesizing and evaluating evidence-based literature and disseminating it out to all stakeholders.

Consumers do not feel that drug surveillance is really generating the evidence they need. CAPA is currently exploring the idea of a consumer driven comprehensive national surveillance system with Health Canada. This proposal will start out small and look at a cohort group of about 100 consumers who are taking biologics. The project will be web-based and look at adverse events with drugs as well as healthcare quality indicators, in consultation with researchers, consumers, government, and industry. The short-term objective is to address the patient's right to know. Why should consumers have to learn about potential side effects of their medication from the main-stream media? The long-term objectives of this pilot project include improving drug safety and efficacy post-market, decreasing the number of deaths and severe side-effects, and approving appropriate prescriptions. Education is a key challenge in getting consumers to benefit from evidence.

Another challenge of evidence is increasing transparency with all stakeholders. We need to know how industry s marketing priorities and government s cost-containment concerns affect the evidence they generate and report. These are areas that need better transparency and perhaps more objectivity. We also need to address the popular media s presentation of contradictory evidence. The very fact that what makes a story newsworthy is that it contains a victim, a villain and a hero means that the evidence is compromised. Recent headlines in mainstream media with regards to arthritis drugs present consumers with very conflicted messages. We need to do more to help them sift through this. And of course, efforts to develop and disseminate evidence are challenged by finite resources.

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Evidence in government decision-making
By Sarah Kramer

It is often assumed that governments do not use evidence either because they are unwilling or incapable of doing so, or for some more nefarious reason. I think that, just as we look for systemic ways to help physicians apply evidence in making their decisions, we should be looking for systemic ways to help government decision-makers use evidence. I do not think there is a lack of will or talent in governments across Canada. However, there are concerns around the tools that are available to us and the sometimes perverse incentives in place.

Government decision making in relation to pharmaceuticals is not just about drug formulary decisions, but also about broader health strategies, resource allocation, ensuring that safety and quality standards are met, and looking at disease management across the spectrum of care. In Nova Scotia, we have a policy review and analysis program for pharmaceutical decisions. While not directly responsible for this process, as the person responsible for ensuring information can be delivered to all decision-makers in the health care system, from the bedside to the Cabinet table, I play a role in helping them make evidence-based decisions. We use a process called DEANS (Drug Evaluation Alliance of Nova Scotia) which brings together consumer groups, academics, government, and others in analyzing and identifying issues around drug practice, current issues and policies, and implementing changes. An important care issue is identified by government, industry, consumer groups or other sources. A policy review is then undertaken in which we all look at solutions and at how they would translate in the real world. A policy solution is adopted and then monitored over time to see if other critical issues arise.

The quality of information

Evidence-based decision-making is information dependent, and information is really not where it needs to be in order to support this process on an on-going basis. Right now, information exists in silos and, as such, supports silo based decision-making. It exists in unanalyzable form, dispersed in charts or in somebody's database somewhere on some floor in some research project. The information is not standardized and, if it is written by a physician, it may be illegible. It is also incomplete and not available in real time so it cannot really support that real-life decision-making which makes the data valid. If the information is being entered by the person who is using it, and if that information is important to them, then it will be valid for a third-party doing surveillance and analysis. If information is entered after the fact and is not crucial to the person entering it, it will be less reliable and less valid. The regular collection of information related to efficacy and outcomes does not exist outside of focused, usually narrow, research efforts. This is a situation that is decried across the health care spectrum, not just in drug therapy. But real world practice is difficult to monitor, so it is difficult to know if a particular decision is improving it.

The electronic health record

There are efforts now at all levels, federal, provincial and local, to build an electronic health record that is driven by the needs of the users at the bedside. It will be real time and important for decision-making at the time of data entry. Rather than follow the provider, it would follow the patient. Nova Scotia's approach to building a health record which is different in form and function but not in the ultimate view from what others are doing across the country is to use common identifiers and standards to build on the existing information systems of different providers and drive each of their information into the data repository that is the live electronic health record. This would then be used to make decisions about a particular patient. Identifiers would then be removed and the information driven into a provincial health data warehouse -- which with good standards could be used nationally -- to provide a really important resource for researchers. We are building into this warehouse some of the important information that does not exist in the healthcare provision, such as disease-based information, CIHI data, Statistics Canada data, data on health status, economic status, and insured services. It will all fit in to build the accountability objectives of government, as well as support evidence-based medicine and policy.

Electronic health records and disease management fit together and are reliant on each other. When we have a complete pharmaceutical history available for a particular patient, we will be able to survey how well that patient is doing, and monitor how well the physician has practiced according to evidence-based guidelines. ICONS is now attempting to survey disease management without an electronic health record, so by necessity they have a silo approach to going out and getting the data.

A balancing act

What government does is balance out competing real demands with finite resources. For example, the evidence can say that, in Nova Scotia, a new cath lab is needed, ICONS is needed, new drugs should be added to the formulary, but the envelope is only so big. The translation of theory into practice also

requires risk-taking. Government perceives the risk as being stacked on their side. It is often difficult to generalize specific research into broader environments, but once a policy or legislative decision is made, it is difficult to pull it back if the real life experience contradicts laboratory-based evidence.

Sarah Kramer is currently the Chief Information Officer for the Department of Health in Nova Scotia. She holds broad responsibility for designing and implementing the province's health information management strategy, including developing frameworks for information technology, privacy policy, data analysis and reporting. Under Sarah's leadership, Nova Scotia has embarked on the implementation of a province-wide, person-specific electronic health record. Sarah also represents Nova Scotia on the national Advisory Committee on Health Infostructure, and is the Chair of the national Electronic Health Record Working Group.