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DRUG INNOVATION AND PATIENT SAFETY THE NEED FOR A NEW PARADIGM

**Proceedings of a Satellite Symposium
held in conjunction with the Second
Canadian Therapeutic Congress**

**April 16, 2005
Vancouver, British Columbia**

SECOND CANADIAN THERAPEUTICS CONGRESS PROCEEDINGS OF A SATELLITE SYMPOSIUM

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DRUG SAFETY: MOVING THE AGENDA FORWARD

Adrian Levy and Stuart MacLeod

Unintended consequences of exposure to chemicals including therapeutic agents have been documented for millennia and undoubtedly occurred, in some form at least, in prehistoric times. In recent decades drug safety has become a prominent feature of the regulatory approval and post marketing surveillance processes. This is not surprising given the increase in the number of new medications available on the market, and substantial increases in medication use coupled with society's lower levels of risk tolerance. Between Jan 1, 1963 and May 31, 2004, at least 41 medications were withdrawn from the Canadian market for safety reasons. To put this in context, at least 2,000 new chemical entities were approved in the same period, a withdrawal rate of approximately 2%.

In recent years, the issue of safe medication use has been garnering even more attention. This is partly explained by recent withdrawal from the market of commonly used medications because of safety concerns, and partly by growing public recognition of adverse events and drug safety as part of the delivery of health care. While patient protection is paramount, we must consistently seek ways of assuring openness to new treatments at the same time balancing the search for therapeutic advance with appropriate vigilance.

The process of evaluating risk associated with new therapies carries through all stages of product development and marketing and is the primary focus of the preclinical testing of new clinical entities. During clinical testing, drug safety must be closely scrutinized by independent monitoring boards. After regulatory approval is granted, post-marketing surveillance is used to ascertain less common effects that may only be identified when large populations use the medication.

Regulation of drug use involves the interdisciplinary application of many types of expertise for assessing drug safety. As a result, the process is complex and multifaceted.

The need for rapid access to efficacious, innovative, and cost-effective medications must be balanced with the need to protect patient safety. Achieving and maintaining balance requires input from many stakeholders and the opportunity for frank dialogue. Stakeholders include at least five groups: the general public, including representatives of patient groups and lay persons; health care professionals; the academic community, including bench scientists and health services and population health researchers; manufacturers; and senior government policy and decision makers. To date, opportunities for regular dialogue among these diverse groups have been scarce and certainly less than optimal.

To address this gap, a half day symposium was held on April 16, 2005 under the auspices of the Second Canadian Therapeutics Congress. The Congress comprised a joint meeting between three associations whose mission is to improve the development, delivery and use of therapeutic substances in Canada: the Canadian Society for Clinical Pharmacology, Canadian Association of Population Therapeutics and Canadian College of Clinical Pharmacy. Within the membership of these organizations are academics, clinicians, students and trainees, executives from industry, and senior policy- and decision-makers.

Careful attention was given to the spectrum of invited speakers: the goal was to have persons representing each group of stakeholders, including the general public. The symposium that resulted comprised a series of balanced, informative and very interesting presentations. A host of ideas for improving drug safety were identified, some involving incremental modifications to the current system and others suggesting more sweeping reforms. This supplement presents a summary of the invited presentations.

The symposium, sponsored by Pfizer Canada Inc, advocates move toward a comprehensive agenda of drug safety and represents an important step in breaking down the communication barriers between stakeholders.

We invite you to read the supplement and consider the issues that were identified and the suggestions to improve the current system. The Canadian Therapeutics Congress is proving itself to be

a valuable forum for discussing issues related to improving the development, delivery and use of therapeutic substances. The issue of drug safety is a common theme around which stakeholders can rally, have directed dialogue, and take action. We think that this model is the only realistic way that all stakeholders can arrive at a consensus to improve the current system while preserving access to promising new treatments.

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DRUG INNOVATION AND PATIENT SAFETY – THE NEED FOR A NEW PARADIGM

A unique multi-stakeholder symposium at the Second Canadian Therapeutics Congress addressed the crucial topic of balancing safe versus fast – how to get new medicines to patients who need them, without jeopardizing patient safety. It yielded some creative, but potentially controversial solutions.

SUMMARY OF PRESENTATIONS

Introduction

The issue of how to balance the need for new drug therapies, and the medical benefits they bring, with an ever-growing demand to ensure patient safety in a risk-averse society was addressed in a satellite symposium held in conjunction with the Second Canadian Therapeutics Congress in Vancouver on April 16, 2005. In unique fashion, the symposium brought together representatives of research, clinical practice, academia, industry, patients and government regulators to discuss this vital topic before an audience of more than 200.

The symposium yielded some unique and potentially controversial suggestions: a sweeping revision to the definition of phase 2 and phase 3 studies and a call (surprisingly not from industry but from a former drug regulator) for accelerated access after phase 2, more responsibility by the media in reporting to patients on safety, greater willingness by industry and other stakeholders to work in partnership with regulators, a review of the system for reporting adverse events in clinical studies, simplification of the informed consent procedure for patients, better and more thorough collection of data on patients and treatment outcomes, particularly in diseases such as HIV/AIDS, and a greater effort to transfer current thinking on the issue into public policy implemented by government regulators.

The session, sponsored by an educational grant from Pfizer Canada Inc., was chaired Drs. Adrian Levy and Stuart MacLeod of the University of British Columbia.

Dr. Robert Peterson, University of British Columbia

Having recently returned to practice as an academic researcher and pediatric clinician from his position as head of the Therapeutic Products Directorate of Health Canada, Dr. Robert Peterson brought a unique perspective to open the discussion. His conclusion: a substantial rethinking of the drug development pathway is needed to address important gaps in each step of the process which makes it unduly cumbersome and expensive without adequately ensuring that proper safety studies are completed before a drug is licensed.

Dr. Peterson noted that while R&D investments by pharmaceutical companies doubled in the decade ending in 2003, the productivity of that investment is diminishing: expenditures are increasing at a greater rate than the number of new chemical entities (NCEs) reaching the application for drug registration stage. This productivity gap, however, is not evenly balanced across the stages of the drug development process. The number of NCEs studied in phase 1 has actually been increasing and few of these are lost going into phase 2. However, the pattern changes dramatically after phase 2, with only half the NCEs proceeding for continued research in phase 3 trials. This key gap must be examined, but the problem does not end there. There is further, and much more important and expensive attrition of NCEs going on from phase 3 to application for registration.

This important attrition rate at all stages of the clinical development process translates into the cost of new products that do reach the Canadian market. Someone must pay – the commercial market. At a cost of \$800 million to bring a new drug to market, the annual budget of the Canadian Institutes of Health Research could not cover the cost of bringing a single new drug to market. This is a powerful argument for not being responsible for new drug development; however, there is a case for becoming engaged in the process, from the perspective of both academic researchers as well as from governments.

The clinical trials that are the basis for the authorization of products that come onto the Canadian market are powered for the evaluation of efficacy, not the evaluation of safety. Safety is based on observations that take place within clinical trials and is highly dependent on the size of the trials, but trials designed to show efficacy are becoming smaller in size, not larger, and likely will diminish even more as they take on a more genomic orientation. The issues

associated with safety are thus going to become more problematic and must be addressed earlier in the drug development process, which at present, due to the regulatory environment, biases the trial designs towards proving efficacy rather than evaluating safety and acts against encouraging trials against active comparators. Further exacerbating this is the environment of commercial secretiveness which, by necessity, accompanies the entire process.

Dr. Peterson outlined the factors which he believes are important for drug development beyond 2005. First, there needs to be greater consideration of the needs of public health in drug development decisions so overall health needs are considered and answered. These include early access to highly promising therapies, availability for special populations including children, full disclosure of all safety information from the development process and some element of cost containment or risk sharing to limit economic exposure. He called for a challenge to the "regulators' rules." The rationale for conducting expensive phase 3 studies has to be reconsidered to determine whether these continue to deliver the information really needed when a product comes to market. Instead, selective conditional marketing approval could be given after more robust phase 2 trials, with the current requirements from phase 3 trials left to "real world" studies within the healthcare system.

Dr. Peterson concluded by saying that such substantive change is necessary to meet the overall objectives of ready access to new therapies, the addressing of unmet health needs and creation of an efficient development process which provides greater safety information and, hence, a better understood risk-benefit profile of new medicines.

Dr. Yola Moride, Université de Montréal

The effective use of risk management assessments and action plans in addressing the issue of drug safety was brought to the debate by epidemiologist Dr. Yola Moride of the University of Montreal. She also outlined how the Canadian provinces could have an important role to play in this process.

She agreed with Dr. Peterson that the current state of drug development and approval means regulators have very little safety information on which to base decisions, because only efficacy data are available from which to detect potential safety signals. Instead, major safety signals are generated by spontaneous reports which are then confirmed, often using

pharmacoepidemiologic methods, possibly resulting in changes in labeling or even withdrawal of the drug.

This information gap could be managed by postponing approval until the full toxicology data become available, but this could lead to unacceptable delays in gaining access to new medicines. A more acceptable alternative is integrating risk management activities throughout the drug development process. Rather than relying on passive pharmacovigilance alone, this could involve systematic epidemiological studies, pharmacovigilance with electronic data transmission and built-in signal detection, and appropriate risk communication as well as commitment to post-approval studies (possibly through conditional approvals). This integrated process must begin early in product development, with epidemiological studies conducted not just to assess the target population for a new drug, but to systematically assess baseline rates of adverse events in the population that will receive it. Once the drug becomes available actual events could then be compared to a known baseline rate. Such information is lacking today and can lead to uninformed and extreme, occasionally catastrophic, regulatory decisions, Dr. Moride said.

Pharmaceutical drug risk management should be seen as the solution to the question of how to optimize the benefit/risk ratio of new medications, providing not just post-marketing safety monitoring, but also continuous updating of effectiveness through evidence-based appropriate use. All regulators would then have access to not just the benefit or risk in isolation, but rather the benefit/risk ratio. Such a system could close the growing gap in delay of drug approvals in Canada compared to the U.S. Dr. Moride showed that not only are fewer new drugs selected for priority review in Canada, but when they are, they take much longer on average to go through what is supposed to be an accelerated process, thus often denying Canadian patients access to important new therapies for considerable periods.

Although drug safety issues at present are often thought of as the domain of the federal government through the role of Health Canada, Dr. Moride discussed the vital role Canadian provinces can play in improved pharmacovigilance and in ensuring appropriate drug usage thanks to their management of provincial drug plans and access to the provincial health databases. These databases can provide valuable information for risk assessment, for evaluating the evidence-based appropriate use of medicines, to generate an accurate denominator for signal detection, to create a baseline rate of adverse events, and to

investigate potential drug-event associations.

At a more clinical level, making the databases more accessible can also help in the creation of risk management action plans that can minimize medication errors, manage controlled access to formularies or exception drug usage, can guide the optimal use of medications in accordance with guidelines and education programs, and can allow development of broader disease management programs that can also be tools for risk management. Dr. Moride also noted that provinces have an important role to play in pharmacovigilance procedures such as mandating the compulsory reporting of adverse events, implementing a program of solicited reporting of adverse events that lead to hospitalizations, requiring follow-up reports on patients experiencing adverse events, and using technology to create an electronic data transmission system with built-in signal generation processes to flag possible dangers. These tools and resources are available, concluded Dr. Moride, and, she said optimistically, Canada has the potential to become a world reference for the implementation and evaluation of risk management plans.

Dr. Craig Hartford, Pfizer Worldwide Development

The industry perspective on the issue, including the approach to drug safety risk management from concept to practice, was addressed by Dr. Craig Hartford, Executive Director and Site Head, Safety and Risk Management in Pfizer Worldwide Development. Dr. Hartford began by stating that Pfizer's goal with respect to risk management is to establish and maintain a favourable drug benefit/risk profile for patients by providing comprehensive and proactive scientifically based methodologies to identify, assess, communicate and minimize risk throughout the lifecycle of a drug.

The core competencies required to achieve this goal, he said, are threefold: the reporting of adverse drug reactions, the analysis and interpretation of those reactions and, thirdly, the synthesis of messages resulting from such risk analyses in the form of an appropriate communication.

The aim is to be transparent about benefit/risk at all times, based on the assumptions that every drug is unique, that no drug is risk free and that safety decisions must be evidence-based. Industry and government are jointly responsible for bringing relevant information forward. He noted that no single information source should be viewed in isolation but rather as part of a comprehensive picture.

Timely communication between pharmaceutical companies, regulators and the medical community is essential to ensure patient safety.

The assessment of benefit/risk is complicated. An underlying factor is the use of differing units of measurement for benefit and risk because efficacy and safety are dissociated. In addition, benefit/risk applies both to the individual as well as to the community and the population as a whole, and these benefit/risks are not always the same. Moreover, as noted by later speakers, benefit/risk will vary with the indication for the product and it will also potentially vary across the lifecycle of a drug.

The new model for risk management, Dr. Hartford said, leans more towards precaution and enhances the role for public and other stakeholder participation as well as further increasing consideration for environmental and social values. The fact is that society now has higher expectations of safety and views the scientific community as just one interested stakeholder in the debate. These changes in the environment mean that industry, academic researchers and the medical community must share accountability with the regulators. Simultaneously, safety monitoring and signal detection tools have improved dramatically, yielding huge quantities of safety data that now must be dealt with.

Cheryl Koehn, Arthritis Consumer Experts

The view of this issue from the patient perspective was eloquently brought to the symposium by Cheryl Koehn, a longtime patient advocate in arthritis and past co-chair of the Canadian Arthritis Network Consumer Advisory Council. Ms. Koehn lives with rheumatoid arthritis and considers herself "a survivor" of the "conundrum" of a healthcare system that needs to aggressively treat the very ill while simultaneously protecting the public. She addressed three areas: drug reporting in the print media, what Canadians have actually said to Health Canada about drug safety, and moving drug innovation and patient safety in Canada forward.

While recognizing that print media can play an important role in informing patients of safety issues, Ms. Koehn wondered if this was actually the case and looked at three print stories published in the week prior to the symposium which, she concluded, illustrate that the media are not living up to this potential important role. One article was on people living with serious illnesses and the second on the supposed inability to prove that increased drug use was providing the kind of

medical benefits manufacturers claim. Rather than focusing on the real world experience of these patients, including safety issues, both articles focused exclusively on cost to the system. A third article about the withdrawal of the arthritis and pain medication Bextra[®], which one would assume would address safety issues, actually provided no useful information to patients who might have been taking the drug concerning the action they should take to find alternative therapy.

The media, Ms. Koehn noted, seem to be less interested or excited about important issues of patient safety per se, but rather thrive on drama and conflict. Patients are often portrayed “as weaklings or scapegoats” and pharmaceutical companies as “profiteers”. Media coverage, she concluded, is not about communicating innovation and patient safety, but rather is about drama, and this itself is putting the public and patients at risk. Ms. Koehn then addressed what Canadians have actually said to Health Canada about drug safety and considered how this information should inform debate on the issue. A survey conducted by Decima Research and released by Health Canada in March 2004, she said, showed 84% of consumers believe prescription drugs are safe and 83% of health professionals feel the same way. As well, 85% of consumers were confident in the system for protecting the safety of prescription drugs. However, she pointed out distressing numbers showing relatively low (about 50%) awareness among health professionals of communications on drug safety issues from Health Canada and pharmaceutical companies. She also noted that the survey showed 82% of consumers believe health professionals should be required to report all adverse drug reactions brought to their attention.

Ms. Koehn concluded with dramatic evidence suggesting that Health Canada must focus on better outreach about drug safety information to patients, health professionals and the public – in that order – particularly in issuing information accessible to those with limited literacy skills. She noted that 22% of adult Canadians fall into the lowest level of literacy, meaning they would have difficulty identifying the correct amount of medicine to give to a child from information on the package. Another 24-26% are in the second lowest level, able to handle only very simple material, while 33% are at the level considered the minimum desirable literacy threshold. Only 20%, or one in five, read at levels indicating that they possess the ability to integrate several sources of information or solve more complex problems. However, she noted, Health Canada advisories to the public on safety issues

are written well above the grade 12 level on the Flesch-Kincaid scale; one had a readability score of 27. As a frame of reference, the Harvard Law Review has a readability score of 30, meaning it is more readable than Health Canada’s public advisories on drug safety issues.

Dr. Julio Montaner, St Paul’s Hospital, Vancouver

The symposium next heard presentations about the balance between drug innovation and drug safety from the point of view of two leading practitioners in therapeutic areas where new drug development is significant, and vital – HIV/AIDS and oncology. The first was an examination of risk and benefit of HIV therapies by Dr. Julio Montaner of St Paul’s Hospital, Vancouver.

A major issue in deciding who with HIV should be treated, and when and how, is the extreme variability of the illness. For exceptional patients, about 1 to 5%, the disease course can be as short as one or two years, while there are others who can survive for even two decades without any evidence of disease progression. Clinicians have also learned to recognize and treat the relatively simple opportunistic infections and conditions, such as oral thrush, which can be early signs of disease progression.

One of the keys to making progress in learning how to treat HIV is the collection and analysis of observational data. Its importance cannot be overemphasized and in a healthcare system that takes responsibility for the health of Canadians, it is unacceptable not to prospectively collect the data which can point to new and better ways to treat patients. This is what happened in the early days of HIV treatments when use of single drugs was seen as ineffective and more aggressive dual therapies, and ultimately triple therapies, were then tried and found more effective. Dr. Montaner also put into context the hopes of developing an HIV vaccine. Given the epidemiological situation in Canada, efficacy of a potential vaccine is obviously important, but safety is paramount.

Unfortunately, the safety of any new HIV vaccine will not be known for decades and it would also take that long again to put in place the infrastructure for an effective vaccine program worldwide. It is important to continue to foster vaccine research, he said, but at the same time the house is on fire and we have to continue to deal with this epidemic therapeutically, over and above prevention. The safety challenge in HIV therapy lies in determining who will benefit most, and when,

from taking potentially toxic HIV medications. The risks of current medications are substantial, so they should not be started when they are not needed, but of course the risks of HIV disease being left untreated and progressing are much greater. The key is to find the right benefit/risk ratio for individual patients. Dr. Montaner showed how, by careful monitoring and studying of data, HIV clinicians were able to refine the definition of who should be treated and when. It turned out that less than half of the patients originally treated actually required immediate treatment. This had a dramatic impact on the goal of improving the outcomes of people with HIV without unnecessarily exposing them to the risk of antiretroviral therapies, while also saving costs.

Dr. Montaner also addressed another important issue related to HIV medications – resistance. To both prevent resistance and ensure optimal outcomes, it is vital that decisions on when to initiate therapy consider the willingness of the patient to commit to therapy. The creation of more fixed dose therapy combinations has helped in this regard, but simpler regimens are still needed. HIV/AIDS is a condition that requires greater than 95% adherence at all times otherwise resistance supervenes, and people who develop resistance have a significantly increased risk of disease progression and death. Simpler regimens, safer and better tolerated drugs are needed so that people can receive treatment on a long-term basis without difficulties.

Given the effectiveness of new therapies in helping patients to live longer, Dr. Montaner noted that more attention must now be paid to safety issues related to long-term use of these drugs. This is an area where much is unknown and where the process is often very poorly monitored. One of the challenges is that a sample size in the range of 20,000 to 30,000 is required to show, for example, whether cardiovascular risk is changed in patients treated with antiretroviral therapy. This demonstrates the need for initiatives at the federal level so that sufficiently large cohorts of patients can be put together that will possibly allow detection of such toxicities before they become a more widespread concern.

The way to optimize the risk of treating HIV patients, Dr. Montaner concluded, is with a comprehensive surveillance mechanism. However, such a system of active surveillance throughout Canada is unfortunately not yet in place.

Dr. Malcolm Moore, University of Toronto

An overview of how drug treatments for malignant

disease are evaluated, and how this may differ from other sub-specialties, was presented by oncologist Dr. Malcolm Moore from the University of Toronto. Many drugs used to treat cancer can have serious toxicity. As a result, drug safety and evaluation of risk/benefit is very important, and strategies are available to alter this ratio.

In oncology, drug safety is generally evaluated in the context of the disease being treated. Clearly, when treating a fatal disease a much higher degree of toxicity is accepted than when treating, for example, a GI motility disorder. Also, treating people who will inevitably die of their disease is very different than treating patients who potentially might survive. Using allogeneic bone marrow transplantation to treat otherwise fatal acute leukemia is an example. The treatment itself may result in 20% mortality, but this may still be considered acceptable when viewed in the context of longer-term survival of those for whom it is successful.

It is also important to consider acute toxicities – such as bone marrow suppression and nausea and vomiting – which are usually manageable, versus chronic cumulative toxicities that are drug specific and generally not preventable or treatable. Now that larger numbers of patients are being cured, more longer-term effects are being seen and these must also be factored into decisions. The greater challenge is with the toxicities that are less predictable. Some are related to treatment, but they can also be related to the disease itself, and this may be difficult to distinguish until data from a comparative trial become available. Frequently, however, the unpleasant effects of the cancers are worse than the toxicity of most treatments. As a general rule if the cancer can be improved, the patient will usually fare better. For oncologists, Dr. Moore noted, phase 3 trials remain fundamental to new drug development.

Over the past 15 years, the administrative and regulatory work associated with new drug trials has increased substantially. However, it is not clear that this has resulted in increased patient safety. If the threshold for reporting serious adverse events is lowered in the interest of gathering more safety data, the danger is that really important events will be missed in the deluge of reports that are either trivial, or probably attributable to the disease rather than the drug. In addition, research advisory boards are increasingly unable to pay attention to the meaning of the data due to its sheer volume. Dr. Moore said he believes informed consent has become an almost useless tool for informing patients about the risks of

therapy in clinical trials. Just as Cheryl Koehn spoke about the difficult readability of Health Canada advisories, informed consent documents are often even less readable and most are more than 10 pages in length. Nobody is looking at the big picture and challenging the value of a long, detailed consent form in terms of helping patients make basic decisions about whether or not to participate in a study.

Dr. Moore also presented an interesting perspective on the very different views of cancer patients towards the risks they are prepared to take and how they will interpret the value of therapy. He is not in favour of living wills because people will often say, while healthy, that they would not accept chemotherapy due to its toxicity. However, if they develop cancer their perspective may change completely.

Dr. Moore concluded by noting that progress in pharmacogenetics holds out great hope for improving assessment of benefit/risk of cancer treatments. For example, in the case of the commonly used drug 5-FU, if the tumor over-expresses thymidylate synthase, the target of this drug, it is very unlikely the drug will be effective. In the future, those determining oncology treatments will be looking at both the host and the tumors to individualize drug therapy and use that as a strategy to minimize risk and maximize benefits for patients.

Diane Gorman, Assistant Deputy Minister, Health Canada

The symposium concluded with comments on the presentations by Diane Gorman, Assistant Deputy Minister of Health responsible for food and drug regulation. She said it is absolutely critical to have this type of dialogue with all the players present. The challenge is to translate the information and ideas presented at the symposium into good public policy. She recognized this as part of her accountability, given the Health Canada mandate to help Canadians maintain and improve their health.

Ms. Gorman cited improvements that have been made in the performance of the Health Products and Food Branch regarding approval time for new medicines in Canada, but also pointed out that federal drug approval is only one element of the process of getting new medicines to patients, starting with drug research and development. She noted that sometimes there are delays between Health Canada approval and the company making the product available on the Canadian market. In addition, the provincial formulary

systems must make formulary listing decisions. The real challenge, she noted, is for all involved to work together in a different kind of relationship to move forward on these issues.

Not just Health Canada, but every player represented at the symposium, she said, has some role in shaping public confidence in regulated drug products. For Canadians to have complete confidence in the drugs they take, they need to have confidence in all the participants in the system that contribute to bringing those products to patients. When issues arise, Canadians often believe that Health Canada either had information it should have acted on earlier, or that it should have had information that it could have acted on. There are some challenges, she said, in terms of who is accountable, who has the information, who should act on the information, and how information can be better shared.

Ms. Gorman also addressed what Cheryl Koehn had earlier described as the “conundrum” faced by the health system and regulator. She quoted from a recent book by Malcolm Sparrow on the challenges of the regulator, in which he advised the regulator to “be less intrusive – but more effective; be kinder and gentler – but don't let the bastards get away with anything; process things quicker – and be more careful next time; be more responsive to the regulated community – but do not be captured by industry”. These paradoxes, she said, give an idea of the world in which the regulator lives.

Ms. Gorman concluded by saying she heard a shared commitment in the room to look for data, to seek evidence, and to act on information throughout the entire system.

A New Paradigm for Drug Safety

Robert Peterson, MD, PhD, MPH
 Clinical Professor, Department of Pediatrics
 Faculty of Medicine, University of British Columbia

Introduction

The objective of this presentation is to present thoughts generated over some years working in drug development and perhaps convey an insight into what can be discovered by close examination of the details of the drug development process. One of the conclusions arising from this inspection is that a substantial rethinking of the drug development process is needed. There are many reasons for this, but when considering these an underlying fact must be kept in mind: that it is the current economic process of drug development that translates into costs of new medicines to the Canadian and other health care systems. We need to examine our expectations of the information that derive from the drug development work that takes place before a product reaches market authorization. Then there must be substantial focus on the knowledge transfer that occurs from the drug development process. This process should make the most of the clinical trial experience and the experience with respect to how decisions are made to allow a product to come onto the market, as well as the process of translating this knowledge into educational information that allow the health care provider to use a new product safely and effectively. Without question, reflection on each of the elements in the process leads to the clear conclusion that there are gaps in each and every step that need to be addressed. Solutions to all questions raised by this examination and concepts as to how to move forward with this will require intensive discussion among all stakeholders

Box 1

The bar for licensing a new drug needs to be changed, it needs to be raised with respect to safety, and this means completing proper safety studies before a drug is licensed.

Some may challenge the aggressive title of this presentation – “A New Paradigm for Drug Safety” – but few would argue that the current status should not be examined. The discussion can start with paraphrasing the editor of *The Lancet*, Richard Horton, who may or may not have it exactly right but nevertheless there is a lot to agree with when he said that the bar for licensing a new drug needs to be raised with respect to safety, which means completing proper safety studies **before** a drug is licensed. This is a substantial challenge, both an economic challenge and an intellectual challenge, to find ways of translating the

knowledge derived in preclinical and clinical development of a drug into actual utilization of that product. Clearly this is an objective that we ought to be moving forward with.

With this as the starting point let us explore possible ways to achieve this objective by examining the various elements and identifying the challenges there will be along the way.

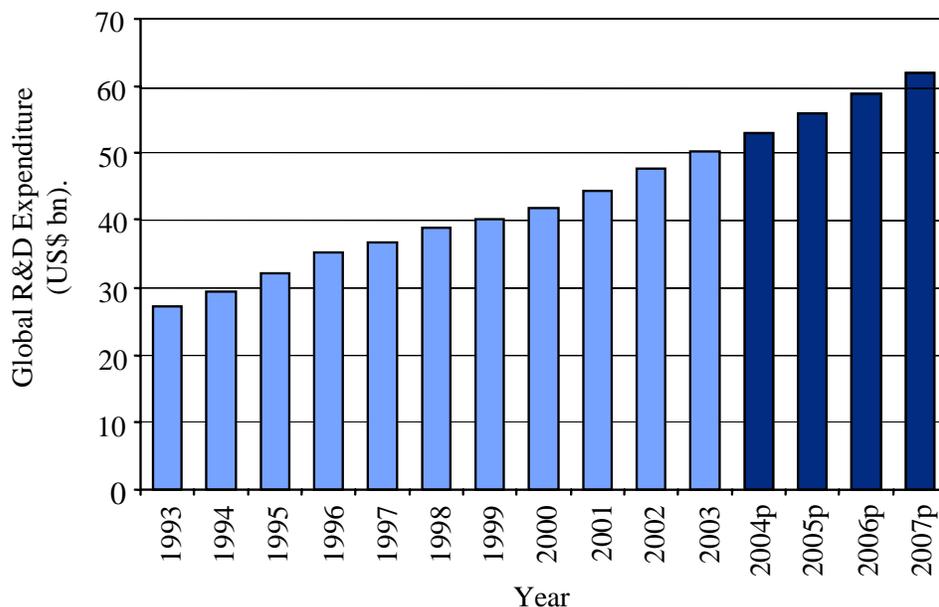
Figure 1 shows data on the global R & D expenditures internationally by pharmaceutical companies, as compiled by the Centre for Medicines Research based on a survey of about 25 market leaders. It shows that expenditures have virtually doubled over the last decade. This has occurred in a setting in which new important drug safety demands that could require additional trials have **not** been introduced. On the way through this discussion about possible changes to the system, it is necessary to keep an eye on the cost of drug development. It is these costs, largely driven by regulatory requirements and the expectations of health care providers and consumers that translate into payment for products when they reach the health care system. However, discussion of the economics of health care delivery will be the focus for more informed individuals.

Positioning Canada to be Competitive in Safe Drug Development

Let us move from the global perspective of investment in R & D to the more focused and perhaps self-serving

question, at least for those of us with careers in drug development, about the process of introducing therapeutic products onto the Canadian market. If there is to be enhanced investment in R & D and changes in expectations, Canadian health care researchers will certainly want to benefit.

FIG. 1 Global pharmaceutical R & D expenditures 1993 – 2007 (projected); used with permission from the Centre for Medicines Research



p = projected figures based on an average annual growth in R&D expenditure between 1997

Without doubt, by far the greatest global R & D investment in drug development is in the United States, where the principle world market for drugs also resides. A competitive market is the European Union, an entity that came into existence specifically to provide a forceful competitive environment to interact with the United States market. Altogether, the US, EU and Japanese markets account for 85% of the global market for pharmaceuticals. If Canada is going to play a significant role in the discussion about safe drug development there will need to be some very specific consideration about how to position ourselves competitively. Canada, with 2% of the world market for pharmaceuticals, is not going to drive change based upon the traditional market forces. However, if there is going to be 50 billion dollars or more invested in R & D it would be agreeable to see a portion of that come into our environment.

Other incentives should be considered if we are to contribute to the rethinking of the drug development process. Possibilities are:

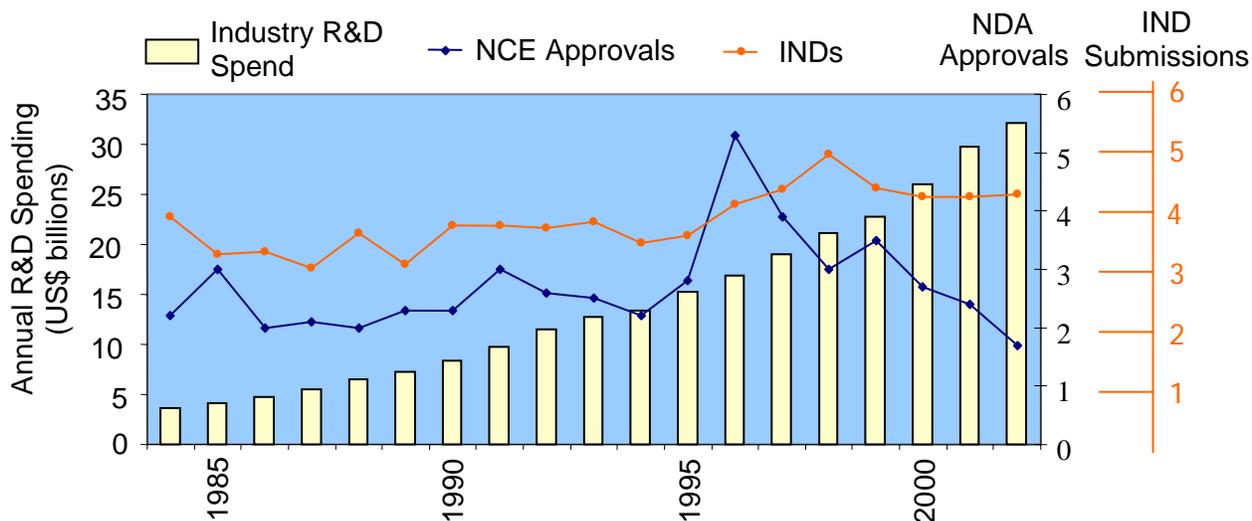
- raise the bar on drug safety
- allow earlier access to new medicines
- leverage Canada's advantage in health delivery
- create an involved, informed customer
- acquire enhanced safety data prior to product approval

The question is how Canada can contribute to a different paradigm of drug development by leveraging its very unique health care system. For one thing, it will be necessary to have much more transparency and openness within the system so that individuals are aware of the available choices when making decisions with their health care providers.

The Productivity Gap

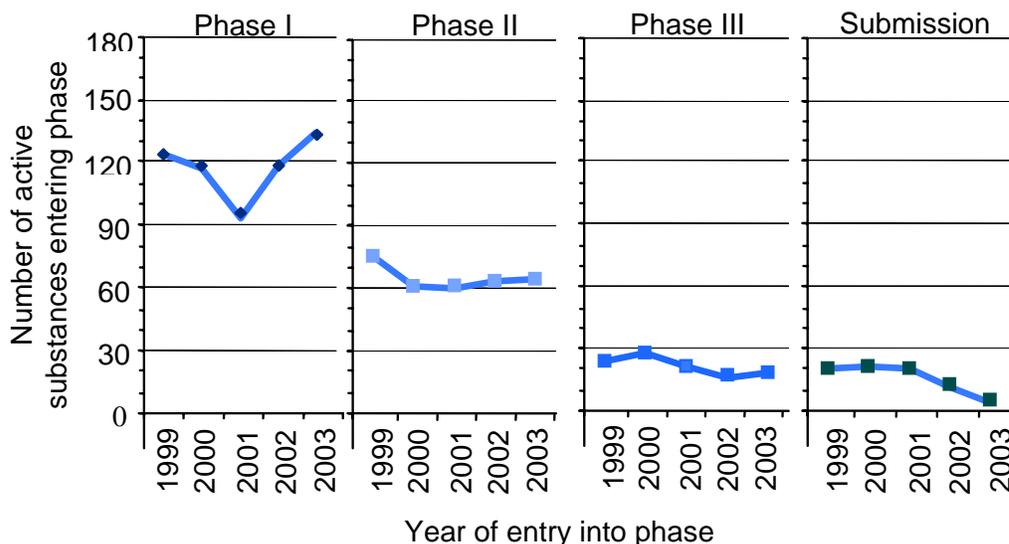
There is the productivity gap in today's system, as illustrated in Figure 2. This figure shows that global expenditures in R & D have been increasing in parallel with the number of applications to conduct clinical trials.

FIG. 2 The productivity gap; used with permission from the Centre for Medicines Research; Data from Parexcel R&D Source Book 2002



In this respect there is fairly good productivity. However, expenditures are increasing at a greater rate than the number of new chemical entities reaching the application for drug registration stage. This is a problem because it means that it is costing more to produce a much smaller number of products. It is important to determine the reasons this is happening and begin to ask questions. Are bad choices being made in the drug development process which drive unnecessary costs?

FIG. 3 Number of active substances entering each phase of development based on data for 27 companies (14 major); used with permission from the Centre for Medicines Research



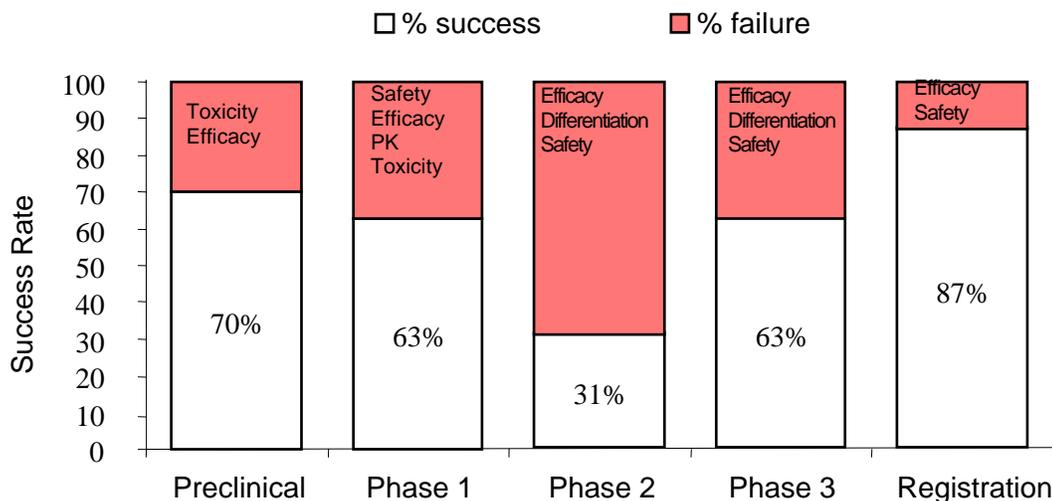
In recent years the number of new chemical entities (NCEs) studied in phase 1 has actually been increasing (Figure 3). Furthermore, despite the fact that a reduced number of NCEs reach the application for approval stage, few are lost going into phase 2. The fact of the matter is that phase 2 work is terrific: there appears to be no difficulty in identifying candidate molecules or therapies. However, the pattern changes drastically after phase 2, with only half the NCEs proceeding for continued research in phase 3 trials. There is no question that this represents a critical gap and it is important that the reasons for this gap are examined closely. Then, moving forward from phase 3, even after spending the hundreds of millions of dollars necessary to bring a product to this point, there is further attrition of NCEs going on to application for registration. All of the efficiencies in this process translate into the cost of the new products that do reach the Canadian market. Somebody is paying, and at the present time that somebody is the commercial market.

It is the pharmaceutical industry that has largely been given the responsibility for the identification, development, and marketing of new products. Government and academic researchers throughout the world have for the most part stepped back from involvement because of the expense. At a cost of US\$800 million dollars to bring a new drug to market, the annual budget of the Canadian Institutes of Health Research could not cover the cost of bringing a single new drug to market. This is a powerful argument for not being responsible for new drug development; however, there is a case for becoming engaged in the process, from the perspective of both academic researchers as well as from governments. I can offer observations and suggestions as a former drug regulator.

Current Realities in Drug Development

The clinical trials that are the basis for the authorization of products that come onto the Canadian market are powered for the evaluation of efficacy, and not the evaluation of safety. As a consequence, safety is based upon observations that take place within clinical trials and is highly dependent on the size of the trials. Economic considerations are causing clinical trials to be smaller and perhaps of shorter duration than ideal for assessment of safety and persistence of efficacy. This means that it may be possible to demonstrate that efficacy persists only as long as the trial continues. It is possible to be very aggressive, very clever, and very intelligent with respect to the design of the clinical trial demonstrating efficacy. At some point in the near future a genomic agenda will be introduced into drug development which will mean that clinical trials will become even smaller because populations studied will be even more homogeneous and efficacy will be demonstrated in these target populations far more effectively.

FIG. 4 Reasons for project failure; used with permission from the Centre for Medicines Research



The problem with this is that safety considerations are rarely tied to the mechanism of efficacy and, as a consequence, as clinical trials get smaller some of the issues associated with safety are going to be more problematic. Safety is a relative term at the time of drug registration, a fact that is a revelation to some people. The general public is unlikely to understand that we are still in the discovery phase in terms of drug safety when a product comes to the market. Products receive authorization based on a positive benefit to risk profile, and the benefit side of the equation is fairly well supported in evidence within clinical trials. While it may be possible to glean some risk information from a clinical trial, the benefit/risk of a product is being evaluated where the risk, the denominator, is somewhat uncertain. Increasing post approval safety surveillance is highly relevant but it is probably not enough. The issue of drug safety will have to be addressed earlier in the drug development process. Throughout this process it will be necessary to focus attention on controlling expenditures on drug development by changing expectations and outcomes.

Some of the economic drivers in drug development are shown in Figure 4. There are four principal reasons why products fail: safety, toxicity, effectiveness, and differentiation. Of particular note is the very high failure rate in phase 2 (Figures 3 and 4). It is at this point that differentiation takes its toll. Differentiation involves commercial decisions and is not necessarily concerned with whether a product will meet an important therapeutic need. Rather, this is a decision based on a commercial entity evaluating the opportunity cost to bring a candidate molecule forward into costly phase 3 studies. The manufacturer must be concerned with return on investment and opportunity costs for all the other candidate products in their pipeline. Decisions to stop moving a candidate forward within the drug development process are not based solely upon its safety and its efficacy. Instead, such decisions relate largely to whether the efficacy demonstrated is now narrowed in terms of what the target population will be based upon the experience in phase 2 trials. It may be that competing products at the time of the decision to launch a phase 3 trial may suggest that other therapies are performing perhaps a little better. Given this reality it is understandable that there is a fair amount of secrecy around drug development. These are decisions that have an impact on billions of dollars of R & D spending and this is reflected in the numerous products that are designed for large markets. The decision to develop such products can be at the expense of products that may be very valuable to health care systems but for which, because government and academic researchers are no longer engaged at the right level of decision making and drug development, never become public knowledge.

It is not the intention here to describe the current drug development phases in detail, but a brief overview will bring the results of the whole process into perspective. To start with, it is important to know that regulators drive the entire process. It is also important to understand that phase 2 research has a very strong influence on proof of concept. At this point in the process the animal work and the phase 1 tolerance studies in healthy volunteers have been done and these lead finally to the question: Does this product work in patients who have the condition for which it is believed to be an effective therapy? Usually phase 2 studies are conducted on several hundred individuals. If the target is a small population, the patients that take part in trials may constitute a relatively high percentage of the total. In phase 2a the objective is proof of concept in patients, usually not in randomized blinded trials. Only quite dramatic toxicity can become evident when the number of participants is this low. Moving to phase 2b, on the basis of experience gained it becomes possible to learn the appropriate dosage for patients. With some proof of concept from phase 2 the process then proceeds to the more expensive phase 3 studies to confirm proof of concept as well as to get additional information about safety. Pivotal trials in phase 3 are powered to accept a type I error of 5%, meaning that there is up to a 5% chance that observed differences are not real but in fact the influence of random statistical variation. For this reason, while the findings of such large pivotal trials usually result in very good publications, the regulator may say "This is really good work, now go out and confirm it" because it is not good enough in the current regulatory environment.

The regulators have a very strong influence in the choices made by pharmaceutical companies. Decisions are being made with the goal of finding the best possible path to get answers that meet regulatory requirements. One must keep in mind that phase 3 trials are very expensive, that there is a high risk of failure, that there are alternative ways to spend the research dollars and, finally, that companies are accountable to stockholders. It is for this reason that the clinical trial environment is quite artificial and that few trials using active comparators are conducted. Again, not surprisingly, all of this takes place in a highly secretive environment.

Given that change in the system is necessary, there are issues that must be considered. First, there is the question of whether the present international regulatory requirements establish the safety of a product when it comes to market. Further, do health care providers have within their knowledge base an understanding of new products that enables them to prescribe judiciously? Likely they do not. Then there is the issue of cost: the traditional three phases of drug development are associated with escalating costs and these translate into escalating prices in the market. The decisions on drug development are not entirely based on the serious unmet needs of the health care system. Consider the recent introduction of a number of so-called lifestyle drugs. Not everybody agrees that there is a category of lifestyle drugs, but keep in mind that these products that are being used by otherwise healthy individuals to impact on some aspect of their lives. These are good market drivers that in some cases turn into profit drivers for companies. This might be acceptable as long as it stimulated the development of other products, but we are not seeing breakthroughs in areas where many believe R & D should be taking place. The bottom line is that researchers, health care providers, consumers, and government should get engaged in some of the decisions that are made.

Drug Development Beyond 2005

There needs to be a greater public health involvement in drug development decisions so that outstanding health needs of the population are considered. This becomes increasingly important as prices escalate and many individuals require drug therapy over the large percentage of their lifetime, for example, in the case of cholesterol lowering drugs, or interventions in children for the treatment of early hypertension. Such prolonged therapy requires that longitudinal studies take place. This is unlikely to happen in a commercial environment. It is not possible to just step back and tell a company that has done the traditional studies that it isn't good enough; rather, do another ten years of follow up, after which regulators will consider approval for marketing. This scenario does not meet any of the demands and it doesn't get products into the health care system for "real-world" evaluation.

Instead, early access to highly promising therapies is called for, along with better data on actual drug utilization and studies in special populations. As a pediatrician, the example of drug therapy for children comes to mind, but there are many other special populations. There is a need for greater public disclosure that is managed in a constructive fashion. Possibly, this should include all the safety information learned during the drug development process. Certainly, there should be no secrecy once a product has reached market authorization and it is being prescribed, paid for, and experienced by patients. There needs to be full disclosure of all of that knowledge in readily available and understandable databases. There will have to be an element of cost containment; price escalation cannot continue. This may necessitate some risk sharing along the way. And finally, new issues associated with safety assessment in actual drug utilization will have to be addressed if we are to move forward.

Challenging the Regulators' "Rules"

The rationale for conducting expensive phase 3 studies will have to be reconsidered to determine whether these deliver today the information really needed when a product comes onto the market. Randomized blinded trials will be necessary but there are instances where the needed information can be gathered within an experience in the health care system rather than leaving this entirely to the commercial world. There is a need for more robust phase 2a proof of concept studies as well as better-organized "real world" studies within the health care system. Planning a cautious, judicious, staggered introduction, utilization and information-gathering around products could be managed in a number of different ways.

ox 2

Drug Development Beyond 2005
<ul style="list-style-type: none"> • greater public health involvement in drug development decisions • earlier access to promising therapies • better data on drug effectiveness (e.g., studies comparing drugs, population safety studies during development) • greater public disclosure • a new paradigm for safety assessment of new drugs • cost containment and risk sharing

Provisional licensing

The regulator could change the regulatory environment by accepting a product on the market under a provisional licensing agreement. The message here would be that this is a promising therapy, that proof of concept is good, and that it has been tested in patients, all of this leading to an acceptable degree of comfort with efficacy. Under these conditions, and especially where there are serious unmet health needs, provisional licensing would provide early access to a promising therapy. In some cases this could probably occur after phase 2 studies are completed. This may appear quite aggressive, but there are products on the market today, not with just provisional licenses but with full market authorization, based on phase 2 studies. These are largely in areas of serious unmet health needs. An example is Iressa[®] for non-small cell cancer, a product that came onto the market a number of years ago following phase 2 studies. Using a purely theoretical example, if presented with the results of a phase 2 study of 300 individuals for whom there are no other treatment options, showing that 280 go into remission, 10 show no effect and 10 may die, it is not reasonable to step back and explain to health care providers, cancer patients, and perhaps to commercial interests why it is now necessary to start a five year program of phase 3 trials to decide whether or not this is a promising therapy. The judicious introduction of systems that will allow such provisional licensing is called for and the health care system should encourage this development.

It will be necessary to start cautiously and to select suitable candidates, especially those that may benefit patients with serious illnesses and unmet health needs. Governments, federal and provincial, as well as payers and other individuals within the health care system would be expected to be part of the discussion. Provided that a good portion of drug development can be integrated into the health care delivery system under a probationary or provisional market authorization with a number of structured requirements, there is the potential to develop datasets in the public domain that are currently not in existence.

Summary

I believe strongly, based on reflection on a career in this area, that we need to reshape and rethink the entire process. There needs to be a greater emphasis on product safety. We need to see both government and academic centres far more engaged as active participants in decisions around drug development. One of the challenges is to determine exactly how this can be accomplished.

Examples presented here are intended to stimulate creative thinking on the part of drug developers, regulators, health care providers, and consumers. Substantive change is necessary to meet the overall objectives of ready access to new therapies, particularly those that address serious unmet health needs, derived from a development program which provides greater safety information and, hence, a better understood risk/benefit profile.

Further reading

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Drug Safety in a Risk Adverse Society: Potential for the Provinces to Provide Evidence-Based Risks and Benefits of Innovative Medicines

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This presentation is concerned with drug safety, the risks of drugs to society, and the potential role of the provinces to ensure drug safety for Canadians. The current environment will be reviewed, but from a more epidemiological perspective than that described by Dr. Peterson, by outlining the parameters that must be taken into account. With this as background, the role of pharmaceutical risk management in the optimization of the risk/benefit ratio of innovative medicines will be discussed, and this in turn will set the stage to suggest a role provinces could play, both by providing resources and by reconsidering the current legislative environment. I will conclude with recommendations that are actually a 'wish list'. All of this will be presented from the perspective of an academic researcher and not on behalf of the Quebec government.

Current Environment

Risk Management Activities Throughout Product Life Cycle

The current state of drug development and the approval process is such that regulators have very little information on which to base decisions. This is basically because, at the time of submission, most often only efficacy data obtained from randomized clinical trials (RCTs) are available. RCTs are of limited value for detecting potential safety signals. The word 'potential' is very important because very often all there is in terms of safety data is based on surrogate end points. Actual adverse clinical outcomes, especially those that are rare, cannot be detected in the context of clinical trials.

Once efficacy data are available there is sufficient information on which to decide on target labels. At the same time, epidemiological studies are conducted mainly to detect the size and the nature of the target population or the baseline burden of illness, and health care utilization in the population that will use the drug. Once a drug is approved for marketing, passive pharmacovigilance based on spontaneous reports is the major safety net to detect drug safety problems. A signal generated by this system leads to an alert and subsequent investigation, often using pharmacoepidemiologic methods and, based on the outcomes, additional review and post approval changes in labeling may be made. In the worst case this may lead to drug suspension or withdrawal. It is obvious that there is an information gap with this system.

Consequences

The extreme risk management strategies, such as product withdrawal or labeling changes, are for catastrophic situations and this is really what we want to move away from. According to a recent review by Lexchin (Canadian Medical Association Journal 2005;172:765-7), 41 products were removed from the Canadian market in the period 1963-2004 for reasons of safety. One way to reduce this attrition would be for regulators to delay approval until the full toxicology data becomes available, but this could take several years or even lead to denial of approval for lack of strong evidence. Such delayed access reduces benefits to patients who are candidates for treatment with the new drugs. Clearly it is imperative that the system be improved. The problem is that excessive reliance on a spontaneous reporting system without the concurrent use of epidemiological tools may lead to poorly informed decisions and ultimately suboptimal patient care. Extreme action should only be taken when the benefit/risk ratio is either unacceptable or unmanageable. The public has come to realize that no drug on the market has zero risk. What people want is more information in order to make better informed choices. A system must be in place for appropriate risk communication.

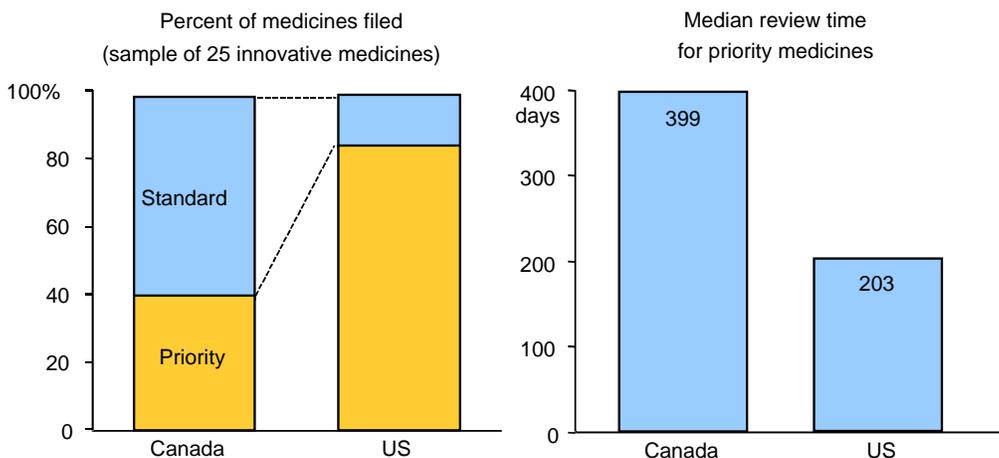
Risk Management Activities in Optimization of Benefit/Risk

Bridging the information gap could be managed through therapeutic drug risk management. Rather than rely on passive pharmacovigilance alone, better safety information could be gathered by adding more proactive pharmacovigilance which is described in terms of a risk management plan. This could involve systematic epidemiological studies, pharmacovigilance with electronic data transmission and built-in signal detection, and appropriate risk communication as well as commitment to post-approval studies. Commitment to conduct post-marketing studies is becoming common in several European countries in the context of conditional approvals. The condition is that the pharmaceutical companies (or their stakeholders) must conduct studies to bridge the information gap by collecting evidence-based benefit/risk information about the drug in question.

Risk management is also very important in the pre-marketing stage because this is when strategies are developed. Epidemiological studies should not be conducted only to assess the size of the target population for the new drug, but also should be done systematically to determine baseline rates of adverse events in the population that will receive the new drug. Then, when a signal occurs in post-marketing surveillance, the expected event rates in this population will provide the correct denominator against which the spontaneous reports can be measured. As the current system works, if there is a spontaneous report of a serious adverse event, and this event is known to happen in a certain type of patient, there are no systematic data that allow us to put this patient profile into the context of the population of users. It is the absence of readily available information when problems do occur that leads to uninformed and extreme, catastrophic regulatory decisions.

Pharmaceutical risk management should be seen as the solution to the question of how to optimize the benefit/risk ratio of new medications. This process involves proactive and systematic monitoring of drug safety in the post-marketing setting. What is really novel is that it offers continuous updating of effectiveness through evidence-based appropriate use of medicines, information that can be made available to regulators. The unit of analysis is no longer just the risk or just the benefit in isolation, but rather the benefit/risk ratio.

FIG. 1 Proportion of drugs receiving priority review in Canada and the US and the average times taken for those reviews. (reproduced with permission from Pfizer Canada Inc)



The gap in Canadian time-to-approval of new medications is increasing, especially compared to the US. Risk management could be a way to provide more information that would make regulators more comfortable when making decisions. Risk management could also have a positive effect on the priority review process. Figure 1 shows recent data from Bain comparing the number of new drugs selected for priority review in Canada compared to the US. Not only are there very significantly fewer drugs selected for the process, but in Canada it has also taken longer for approval of the drugs that did go through this accelerated process.

Currently, risk management strategies are developed based on guidance papers. Such documents were recently finalized by the FDA, and there are also European guidances developed by the European Medicines Agency Pharmacovigilance Working Party. As well, the International Committee on Harmonization E2E is focused on pharmacovigilance.

To summarize before moving on to the role of the provinces, there are two main activities of risk management, risk assessment and risk minimization. The former is conducted mainly through pharmaco-epidemiological studies and also through the solicited reporting of adverse reactions. Passive collection of pharmacovigilance data is no longer sufficient and the challenge is to actively search for adverse events while monitoring drug utilization in the real-world setting. Risk minimization activities are accomplished through interventions that are commonly referred to as 'RiskMAPs' (risk minimization action plans). These include targeted education and reminder systems or, more aggressively, Performance Linked Access Systems.

Provincial Responsibilities

Current provincial responsibilities include controlling drug dispensing and optimizing drug usage. As part of the drug programs, provinces maintain claims databases of prescriptions and medical services. They also have various schemes to limit access to certain medications with the goal of controlling usage-driven costs. Examples are generically referred to as the exception formulary (Quebec) and the therapeutic intent formulary (Ontario and Manitoba). Most of the drugs that are on such exception formularies are there because of cost – to prevent new medications from being used inappropriately as first line therapies. Other drugs, such as acyclovir, are on the formulary for safety reasons but such drugs make up a minor proportion.

In Quebec right now there is a new legislative environment that will set the stage for much more proactivity in the area of risk management and drug safety. The Minister of Health is currently developing a drug policy that is geared toward optimizing drug use and will be the foundation of a system to ensure that drugs have appropriate benefit/risk ratios. There is also Bill 90 which focuses on the interdisciplinary aspects among the various health professionals. Instead of having front-end health care as we now have, health care will be delivered as a continuum, with patients being followed by health care professionals working in teams in order to optimize treatment.

Resources

For the past few decades administrative databases have been used to monitor drug utilization as well as to conduct risk assessment and effectiveness studies. In addition to this, in Quebec there is Bill 83 which states that all patient health data will be accessible to all health professionals electronically. This means that a pharmacist who wants to dispense a drug will, in theory, have access to the entire patient dossier. Although at a very embryonic stage at the moment, this one day will be the norm.

The various databases can be linked to obtain individual patient data on drug acquisitions, health service usage, or adverse events that are documented in the system. When these databases provide insufficient information, it is possible to link to hospital charts or even patient questionnaires to access additional data. This is currently done mainly in specific research projects, but when Bill 83 comes into effect such linkages will be routine and the information will be available to all health care professionals. Working with databases, monitoring drug use, and having access to patient information have been going on for some time. What is new in the context of risk management is that it is now going to be possible to work with specific target risks. The risks suspected in phase 2 or phase 3 of drug development will become part of the regulatory process, for example in situations of conditional approval. What is new is that it will be a proactive, systematic, iterative process that will focus on the benefits/risks of drugs. The individual components are already in place; it is the packaging that is new.

Box 1

Risk Management Activities

Risk Assessment

- pharmacoepidemiologic studies
- solicited reporting
- monitoring of drug utilization

Risk Minimization through interventions (RiskMAPs)

- targeted education & outreach
- reminder systems
- Performance-Linked Access System

Potential Role of Provinces

The provinces will have a role in each of the major activities, whether it is pharmacovigilance, risk assessment, or RiskMAPs.

Mandatory reporting includes serious effects of all drugs as well as all events with new drugs. As for solicited reporting, in Quebec right now the regional centre for pharmacovigilance employs only one person. To do solicited reporting properly there should be a team that actively seeks adverse drug reactions in hospitals, because this is where patients with serious adverse events are likely to be found. Physicians do not always suspect that an event might be drug-related. Data from countries in which solicited reporting has been implemented show that this is a very efficient way of collecting serious adverse events.

Box 2

Potential Role of Provinces

Pharmacovigilance

- mandatory reporting: serious effects, new drugs
- solicited reporting (e.g., hospital)
- active query
- electronic data transmission with built-in signal generation processes

Risk Assessment

- administrative databases
 - risk assessment
 - evidence-based appropriate use of medicines
 - accurate denominator for signal detection
 - baseline rate of adverse events
 - investigate potential drug-event associations

Risk Management Action Plans

- minimize medication errors
 - electronic formulary
- controlled access
 - exception formulary
 - therapeutic intent
- optimal use of medications
 - prescription guides and education programs
- Law 90 and 83 will facilitate implementation of performance-linked access programs

After an event is reported, active follow-up is very important to document what subsequently happens to the patient. This will be facilitated by electronic data transmission (through Bill 83) because health professionals will have access to information about the patient's drug history, for example. In order to work from a pharmacovigilance perspective there should also be a built-in signal generation system. This is not in place currently and there is a potential here for more provincial involvement.

Administrative databases can provide data on evidence-based appropriate use of medication and accurate denominators for signal detection in terms of patient profiles and patterns of drug use. As well, these databases give baseline rates of adverse events and allow investigation of potential drug events and associations once an alert or signal has been generated. These capabilities are currently in place; however, what is not in place is the proactive, systematic, comprehensive component.

In the risk management action plans arena it is possible to minimize medication errors. An important source of adverse drug reactions is from drugs dispensed by electronic prescription. In the US all prescriptions will be electronic by the year 2009, and this will also be implemented as part of Bill 83 in Quebec.

Controlled access, whether it is determined by an exception formulary or by limitations based on therapeutic intent, is a very strong tool because it gives access to data on indication for drug use. This extremely important information, which is currently not available in the administrative databases, will allow assessment of the background rate in a specific population of patients. It can also be used simply for assessment of the risk associated with a particular drug. Without the indication it can be very difficult to control for different patterns of drug use based on different indications. The formulary exceptions system used in Quebec requires the physician to complete a cumbersome volume of paperwork, and many drugs that could have potential benefits are not prescribed for this reason. The therapeutic intent system in Ontario is more physician-friendly: to authorize dispensing it is necessary only to check off which requirement is met from a printed list of options. Efforts to optimize use of medications will continue through prescription guidelines and education programs. Bill 90 concerning the multidisciplinary

team approach, and Bill 83 concerning electronic data transmission will facilitate the implementation of Performance Linked Access Programs. For, example if a drug has been found in phase 2 to prolong the QT interval, patients may be required to have had an electrocardiogram before certain drugs are dispensed. Then there is the problem of the information loop among the pharmacist, the person who performs the electrocardiogram and the prescriber (who may not have ordered the electrocardiogram). Electronic data transmission and availability of electronic patient charts would facilitate the implementation of such programs.

Disease management programs to enable the follow-up of patients through the continuum of care are being put into place within context of Bill 90. These programs can be a tool for risk management, especially through family physicians who are increasingly acting in the capacity of case managers.

Challenges

In summary, the tools and the resources are available and the legislative environment, especially in Quebec, is setting the stage. However, research needs include:

- development of a system to ensure systematic and proactive risk assessment
- methods to evaluate effectiveness of RiskMAPs to assure that goals are being achieved
- development of a platform for the exchange of information among all stakeholders
- design of an iterative loop process for the continuous assessment of evidence-based benefit/risk

The provinces should be considered active partners in risk management and should be part of any national advisory committee established to discuss risk management. Currently, Health Canada has a problem with the conditional approval because follow-up requires a lot of resources. Provincial data and expertise could contribute resources for such follow-up.

The risk management paradigm sets a new standard of evidence for benefit/risk assessment of innovative medicines. It can effectively balance regulatory actions leading to better care for patients. My view is very optimistic. Canada is not a big market in the drug arena but it certainly has the potential to become a world reference for the implementation and evaluation of risk management plans.

Further reading

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An Industry Perspective on Clinical Drug Safety Risk Management: From Concept to Practice

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Introduction

Drawing on a variety of sources, this presentation will overview the changing paradigm of clinical drug safety risk management. It will also touch on drug safety signal detection as a whole and how to move the drug safety risk management agenda forward through risk management plans that identify and address gaps in safety knowledge.

No talk on safety risk management is complete without a definition. Industry generated a definition some years back and shared this information with regulators. We are pleased to report that some of these concepts have evolved into the FDA guidance statements concerning risk management. The definition states that the goal of safety risk management is to establish and maintain a favourable benefit/risk profile in patients, and that the objective is to provide comprehensive and proactive scientifically based methodologies to identify, assess, communicate and minimize risk throughout the life cycle of a drug. In considering this definition it is important to keep in mind that risk can be both real and hypothetical.

In any mature organization there are typically three competencies around safety and risk management (Figure 1). The first is the reporting of adverse drug reactions, the second is the analysis and interpretation of those reactions, and the third is the synthesis of those messages into a communicative form suitable for dissemination. The aim throughout is to have appropriate transparency about benefit/risk across the life cycle of a drug.

FIG. 1 Core safety risk management competencies in a mature organization



Key Risk Management Assumptions

Certain assumptions form the basis of any risk management discussions. The first is that each new drug is unique. The second is that no drug is risk free, but the risks can be evaluated and managed. Thirdly, safety decisions must be evidence-based; industry is jointly responsible for bringing such information forward. It is also important that no individual information source should be viewed in isolation, rather as part of the picture as a whole. Finally, timely bilateral communication among pharmaceutical companies, the regulators and the medical community is essential

to ensure patient safety and to ensure that there are no surprises concerning benefit/risk. Benefit/risk assessment is complicated for a number of reasons. To begin with, the units of measurement for benefit and risk differ because efficacy and safety are measured differently. In addition, benefit/risk applies both to the individual as well as to the community and the population as a whole, and these benefit/risks are not always necessarily the same. Moreover, benefit/risk will vary with the indication for the product, and potentially across the life cycle of a drug.

The safety risk management paradigm has changed; one is reminded of the ostrich with its head in the sand and a lion about to make a meal of the ostrich: In the past the industry has been perceived by some to have buried its head in the sand with respect to safety, with the attitude of ‘what we don’t know can’t hurt us’, but that has evolved into the new paradigm of ‘what we know makes us strong’ in the safety arena.

New Model for Risk Management

The new model encourages regard for precaution. It promotes public and other stakeholder participation as well as takes into account environmental and social values as a whole. There is recognition that science is just one facet: scientific results are under much scrutiny and their credibility is increasingly questioned, which does not mean that they are not credible, but it is recognition that scientists are only one of many sources to be consulted in the risk management process. There is a need to share this increased responsibility with regulators. Both consumers and health care practitioners typically see regulatory authorities as the optimal point through which adverse drug reaction information should be collected, interpreted and communicated. But it is unlikely that the regulators can manage this alone, particularly with ever-increasing safety demands. Here is an opportunity for industry, academia, and the medical community to work together with regulators. It is obvious that the use of new technologies is going to be important as we go forward, particularly in the areas of safety and efficacy biomarkers as well as in pharmacogenomics.

Box 1

<p>A New Model Emerging for Risk Management</p> <ul style="list-style-type: none"> • increased regard for precaution • enhanced public and stakeholder involvement • takes into account environmental and social values • scientists & scientific results regarded as only one of many sources to be consulted • more open communication of safety and risk management strategies and decisions • increased focus on impact analyses and carefully considered risk communication strategies • sharing the increased responsibility of the regulators: support by industry, academia, medical community • use of new technologies: safety and efficacy biomarkers, pharmacogenomics, information technology <p>[adapted from Lofstedt, R.]</p>
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Most professionals are aware of the recent regulatory focus on risk management, including PDUFA III, FDA guidance documents, ICH E2E (which Canada inputs to), and CIOMS VI. But there is also a non-regulatory focus. It is not just legislation that has led us to the risk management paradigm of today. People are living longer and there is a wider variety of drugs to treat a wider variety of diseases. This means that there is greater exposure to drugs within the population. Along with these changes to the safety landscape there have been a number of drug license withdrawals, usually initiated by regulators, but some spontaneously executed by the industry.

One result is that public expectations of safety are much higher than previously. A significant component to this is media driven and, as is also true for all individual stakeholder perceptions, there is the potential to yield unbalanced viewpoints. At the same time signal detection tools are improving substantially, increasing the specificity or sensitivity with which safety signals can be detected, for example, by using Bayesian algorithms and proportional reporting ratios. Improved electronic information tools are helping the safety reporting and analysis process, but simultaneously producing huge quantities of safety data to be dealt with. A discussion of risk management obliges

mention of the precautionary principle. In its simplest form this principle says ‘first do no harm’, and in principle this is a respectable idea. But there is reason for caution: in certain modes of implementation the precautionary principle may be problematic, and the result could be that we are “safe and sorry”. There are emerging comments (for example, Financial Times, 25 February 2005, page 8) that the regulator’s role in protecting consumers may come at the cost of developing new therapies. I would advocate that the responsibility for keeping alive innovation in research and development of new chemical entities should be a shared responsibility.

Risk is all about perception in many ways, and management of risk is not a new concept to the pharmaceutical industry, nor is the understanding of acceptable risk and tolerability. Moreover, other industries have been dealing with risk management for many years, including the nuclear, military and transport industries, all of which frequently make cumulative decisions with regulators about risk on a regular basis. For drug therapies cultural aspects play a very influential role concerning the acceptance of risk. This aspect is a real challenge, in particular as risk management plans largely need to be viewed as global. For example, what affects the safety of a population in Canada must be taken into consideration in preparing and implementing risk management plans in Europe and vice versa. In the end, the objective is to find an ideal limit of tolerability, the point beyond which it is inappropriate to continue. Some consider that this point is not in practice likely to be zero risk, rather it could be negligible, unimportant or tolerable risk.

The importance of consultation and communication between the drug industry, drug regulators, academia, prescribers and patient groups around risk management cannot be overemphasized. In fact, pharmaceutical industries have played an important role in advancing this area. For example, Pfizer’s personnel have held a number of leadership positions on relevant working groups and other committees, including Head, Risk Management Working Group (PhRMA) of the Pharmaceutical Innovation Steering Committee and Chair, Action Group on Risk Management for the European Federation of Pharmaceutical Industries, as well as Past President, International Society for Pharmacoepidemiology (ISPE). Altogether we are involved in more than a dozen such organizations. These examples demonstrate that industry has been and remains an integral part of the process furthering the understanding of risk management.

Internal Risk Management Committees and Safety Review Teams

Most pharmaceutical companies have some form of safety review team or risk management committee. The scope of their responsibilities usually goes beyond the regulatory paradigm for the simple reason that patient safety is good business. Some of the activities in which an internal risk management committee would typically become involved are listed in the sidebar. Although the submission of risk management plans to regulators is now mandatory, this is not new to industry and some companies have been generating similar plans for several years.

Box 2

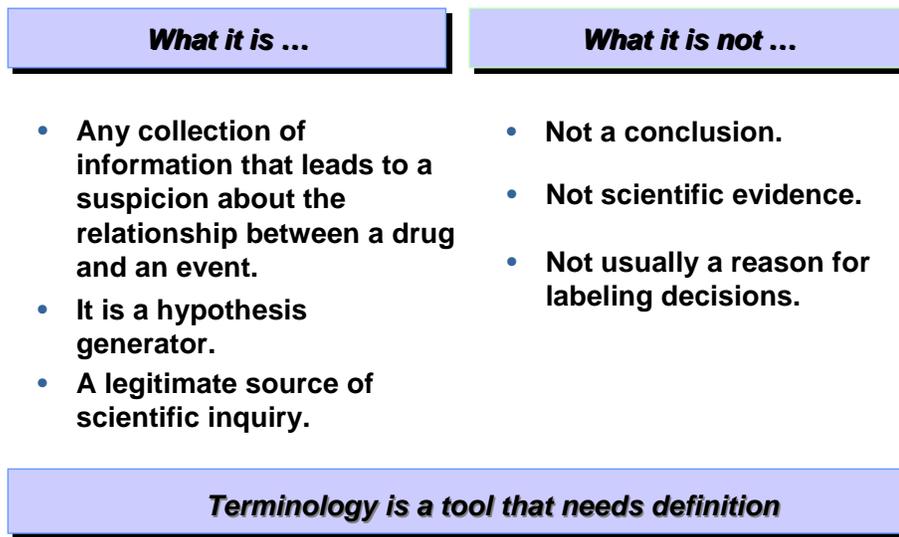
Typical Internal Risk Management Committee Activities

- real-time and cumulative safety reviews in preclinical and clinical studies
- survey data from similar compounds under development
- communicate safety data to teams with parallel indications/products
- maintain logs of agreed risk assessments and actions
- establish internal Drug Safety Monitoring Committees as appropriate
- develop risk management positions, epidemiology reports and safety studies
- enhance safety biomarker awareness (including pharmacogenomic safety and efficacy markers)
- regular updates to Investigator Brochure benefit-risk/safety sections
- ensure risk is adequately addressed in key documents, e.g., Common Technical Document’s Summary of Clinical Safety and Clinical Overview, Label
- maintain, coordinate and update the risk management plan
- ongoing review of post-marketing safety data
- ensure that commitments made in the risk management plan are executed
- safety issues management: recommend plan of action in collaboration with stakeholders

Safety Signals and Databases

A safety signal can arise from any collection of information that leads to the suspicion of a relationship between a drug and an event (Figure 2). The relationship may not necessarily be causal. Safety signals serve as hypothesis generators and are a legitimate source for further inquiry. However, such signals do not provide conclusive scientific evidence of a safety issue and are usually not a reason for making decisions about, for example, labeling. One of the reasons for this is that signals come from databases and there are many types of databases. Spontaneously reported data, for example, is largely an undefined universe of data that, although it can serve as a signal generator, is sensitive to stimulated reporting. The resulting data do not give the true incidence of adverse events, if only because of under-reporting. Furthermore, data collected in this way cannot easily be validly used for comparisons between drugs or for hypothesis testing.

FIG. 2 **What is a “Signal”?**



On the other hand, scientifically collected information offer a well-defined universe of data that is not affected by stimulated reporting in well-designed studies. These data can be used to test safety hypotheses or to compare rates of adverse events between drugs. However, they are not useful for identifying rare events because of inadequate sample size, short study durations and restrictions to selected populations.

Risk Management Strategies and Plans

The key components to any drug development risk management strategy are described in any current pertaining regulatory guideline. The typical strategy document begins with a summary of the known important safety information about the drug and then proceeds to identify the issues and gaps in knowledge. This is the so-named “pharmacovigilance specification”. The next step involves proposals as to how the gaps should be filled, the so called “pharmacovigilance plan”. In the course of generating a strategy a continued review of benefit/risk is very important and involves assessment, communication, and transparency about the benefit/risk of the product.

Speaking of gaps brings to mind special populations and the fact that pediatric pharmacovigilance is a particular concern to many. Without doubt safety in children is becoming increasingly important as existing and novel therapies become more widely indicated for children. To begin with, children are passive participants. They are not small adults and drug pharmacokinetics and pharmacodynamics vary substantially from adults in certain cases. Requirements for pediatric data have increased in recent years and triggered the need for more formal clinical trials. To date the drug industry has been fairly responsible about including known information about clinical pediatric

dosages in labels despite the fact that this is not always required. One reason for concern is potential safety issues in the longer term in children receiving drugs during their growth and development phases. Safety assessment in children is made difficult by the low overall drug exposure from relatively small databases and the unique difficulties in collecting data in the post-marketing period. If a safety signal is identified the immediate concern is confirmation, because at most stages it is a potential safety issue rather than an identified safety hazard of known risk. This is usually done through routine pharmacovigilance; however, enhanced pharmacovigilance may be necessary to verify or refute a safety signal.

Pharmacovigilance Assessment/Monitoring Tools

Examples of tools used in safety pharmacovigilance can be divided according to whether they are standard or more specialized (enhanced pharmacovigilance).

Spontaneous reporting has already been mentioned and includes reports from the medical and scientific literature. Periodic Safety Update Reports and other Annual Safety Reports are the usual communication methods.

More specialized pharmacovigilance can involve stimulating accelerated reporting of spontaneous events and compiling adverse event report summaries more frequently than is typically required by regulators. Data capture aids are a very useful mechanism by which to increase the quality of reported information in real time, and collection of epidemiology-based data more than ever has a pivotal role in enhancing our understanding of potential safety signals. The databases that allow examination of background rates in disease are helpful.

Box 3

<p>Pharmacovigilance Plan: Assessment/Monitoring Methods</p>
<p>Routine (standard) pharmacovigilance</p> <ul style="list-style-type: none"> • spontaneous reporting, including reports in the literature • Periodic Safety Update Reports, Annual Safety Reports
<p>Special (enhanced) pharmacovigilance</p> <ul style="list-style-type: none"> • accelerated reporting of spontaneous events • follow-up specific case reports • specific reviews of class labels • more frequent adverse event report summaries • data capture aids • epidemiology <ul style="list-style-type: none"> - databases (for drug and background rates) -patient surveys (cross sectional study) -registries -other observational (case control and large cohort)

However, some databases populate slowly and in other cases background rates produce too high a level of noise. For example, myocardial infarction occurs relatively commonly and may or may not be attributable to a drug being taken by a patient. If the background incidence in a database is high, then recognizing a signal for myocardial infarction potentially attributable to a drug becomes more difficult.

Patient surveys and registries are also options. Caution is prudent when setting up a registry: careful consideration must be given to the specificity of the questions being asked, otherwise the registry design may not yield valid answers. Other epidemiological observational studies such as case control studies and large cohort studies are all useful specialized ways of collecting enhanced pharmacovigilance data.

Risk Minimization

Once a safety issue (confirmed safety hazard, known risk) is identified from the verification process following a safety signal, the next step is risk minimization. Clearly, dialogue and communication with health authorities and other stakeholders is important. Updating the licensed prescribing information (labeling) is also a valuable method of informing professionals, and printing new high safety risk information in special black boxes or bold letters makes changes more evident. In the last few years the efficacy of such labeling has been questioned and researched in-part; many think that the label remains a robust risk minimization tool. Patient package inserts/information leaflets can be used as an existing (or new, in some regions) tool. Other means of education used to minimize risk are through news releases, including information targeted directly at the public and special letters targeted at patients and healthcare providers. Supporting education by health practitioners is also a useful option, as are educational guidelines from pharmacists. In regard to education, Health Canada can be perceived as one of the world regulatory leaders in publishing adverse reaction newsletters, effecting targeted advisories and warnings, and “dear healthcare provider” letters. The pharmaceutical industry and regulators both use “dear health care provider letters” to minimize risk.

More stringent or severe risk management interventions may be considered if educational methods do not achieve their objective, or if there is serious concern about the benefit/risk. It is important that these special interventions be targeted at the specific safety issue concerned: use of the more severe methods should not result in inappropriate denial of access to the drug. It should be kept in mind that risk minimization tools can be a temporary measure whilst more data is being collected. None of the special interventions listed here are particularly new to the risk minimization scene, but they can have major impacts on those who implement them. It is important to stress that the effectiveness of these interventions should be measured. Evaluation of the tools and evaluation of the effect of using the tools on the risk minimization objective must be carried out if the effectiveness is to be fully understood.

Summary

There is an increasing focus on pan drug life cycle safety risk management in the pharmaceutical industry and the demonstration thereof to both regulatory authorities and patients. Without doubt this is a positive trend in the best interests of patients, health practitioners, regulators, and the drug industry. It allows for therapy to be more individualized and improves drug safety. Well designed risk assessment plans should ensure more rapid regulator

Box 4

Risk Management Action Plan Basic Interventions

- dialogue/communication with health authorities
- label changes (black box/bolding)
- patient package inserts
- education
 - news releases, adverse event newsletters
 - patient information
 - targeted letters, e.g., Dear Patient/Doctor/Pharmacist/Nurse
 - support education by health practitioners
 - medication guides from pharmacist

Risk Management/Minimization Action Plan Special Interventions

Characteristics:

- targeted at the potential specific safety issue
- should not result in inappropriate inhibition of access
- may be considered temporary measures
- require metrics on effectiveness of risk minimization tool

Intervention Options Kit:

- reminder systems (prompts, reminders)
- restricted prescribing (e.g., only specialists)
- restricted distribution
- informed consent by patients
- requiring doctors/pharmacists to attest to understanding the risks
- limit refills
- limit quantity
- special packaging/sticky labels
- required assessment before prescription (e.g., known hepatic or renal status)

and reimbursement approval, which is important to the commercial viability of many drugs, while at the same time result in low or well-controlled risks. There is also an important impact on resources, not just for the industry but also for everyone in the health care system, and the effect becomes greater and greater as the number of risk minimization plans implemented increases. Here is an opportunity here for sharing of resources, experience, and skills among all stakeholders to effect the new global risk management paradigm that is on our doorstep. The pharmaceutical industry supports and is advancing safety and risk management through innovation, for example through development of signal detection tools, and through collaboration, for example the development of joint crisis management approaches, and the development of risk minimization action plans.

Further reading

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Drug Innovation and Patient Safety in Canada: A Patient's Perspective

Cheryl Koehn

President, Arthritis Consumer Experts

Past co-chair, Canadian Arthritis Network Consumer Advisory Council

Person with rheumatoid arthritis

I'm honoured to be on a panel with such heavy hitters. I certainly don't view myself as one. In fact I'm always surprised when I get invitations to speak in front of groups like this. What I think that means from an advocate's perspective is that I'm being too nice. So, I'm going to have to work next week on toughening up my act a bit. Last night at the reception I had an excellent piece of advice from someone that I respect a lot, an academic, and he said "Whatever you do Cheryl, when you get up there, don't rant". Had he given me that advice three hours earlier when I handed my slides over to the technician it would have been really helpful. So, if at any point in time a thought bubble comes up above your head and it says "Oh my god she's ranting", just edit the word rant and put passion in there. That would be really helpful.

I am here to talk about my own views as a person living with a chronic disease. I consider myself a survivor, as do millions of patients in this country. We view ourselves as survivors and I think we do so because we live in not ideal times from a health care system perspective, at least as far as the issues of drug innovation and patient safety in Canada are concerned.

We are faced with a conundrum and have been for a long time, the conundrum that exists between drug innovation and patient safety. The conundrum is that we have people such as those in the audience, the generally "healthy" public, and we want to protect these people – most certainly – while serving the needs of people with severe crippling disease. Figure 1 shows the outcome of moderate to severe rheumatoid arthritis. The evidence is now crystal clear that the processes that result in crippling begins as early as six weeks after disease onset, including ulnar deviation, nodule development and possible systemic complications of a disease that is thought quite innocuous by society. The only thing proven to stop this process, except of course spontaneous remission, which occurs in ten percent or less of people with rheumatoid or inflammatory arthritis, is drug therapy. The evidence is irrefutable. So that's the conundrum: how do we aggressively treat the very ill who have debilitating and potentially life threatening disease with innovative medicines while protecting the public from unanticipated toxicities.

FIG. 1 Hands of a person with rheumatoid arthritis



This presentation will focus on three things that I believe are central to the topic of drug innovation and patient safety.

- drugs in the print media;
- what Canadians have actually said to Health Canada about drug safety;
- moving drug innovation and patient safety in Canada forward.

I hope to do so in an as evidence-based way as possible, knowing that those in the audience are very passionate about working to create a body of literature on which evidence based decisions can be made.

Drugs in the Print Media

What are the public, and obviously patients as part of the public, hearing or reading in terms of drug innovation and safety in Canada? The answer is whatever Canada's leading health researcher wants them to hear – Andre Picard, health reporter for the Globe and Mail. Of course, the print media plays a very important role in shaping public perception and it **can** play an important role in informing patients of safety issues. The question is whether it does and the answer may be found by examining three articles that appeared in the print media last week over a three-day period.

The first article focuses, importantly I think, on consumers who actually are responsible for the lion's share of expenditures on medications or at least consume that share. It was reported that 40% of high cost users have high blood pressure, 25% have diabetes, etc. The bottom line is that high cost users are really sick. In this piece, while it is noted in one phrase that these people are sick, the main point was, sick people could be more vigilant about overuse of prescription medications. This article is about intervening in terms of cost; there is no mention of patient outcomes. What kinds of outcomes are being achieved in these high cost users? There is also no discussion about patient safety or appropriateness of treatment – it is simply about cost.

The next article again focuses on cost. The previous article and this one actually appeared side by side. In the second, the reporter comments that, while prescription drug makers claim that many treatments are cost effective because they keep patients out of hospital, there is no way of determining if this is actually true in the real world. If this is true, then what has happened to all of the peptic ulcers that required surgery before H2 receptor antagonists were marketed? Why is the incidence of cardiovascular disease in the US declining and why are cardiovascular outcomes improving? In my own area of interest, why has lupus, which was once nearly uniformly fatal, become a disease that has doctors worrying about the quality of life for their patients and not death? Why has rheumatoid vasculitis and Felty's syndrome virtually disappeared? This is **real world experience** and we are seeing it and we are tracking it and patients are living better lives because of the drug innovation that has occurred globally.

The third article, one that is obviously of interest to many in the audience, is about the recent news about Bextra[®]. This article ran under the banner of drug safety, and has relatively good information about not starting on Bextra[®]. The table that accompanied the piece reported the numbers of patients on Bextra[®], prescriptions written and prescriptions filled. While there were many people taking this drug immediately prior to the publication of the article, there was no information about what to do. The only time the word "safety" was used in the article was when the writer stated that Health Canada's "...safety review of COX-2 inhibitors should be completed by the end of this month". The question that needed to be answered by this article was, what should a person was using Bextra[®] do today? Sure, Health Canada is going to convene a panel so that the public and scientists can have their say on the matter, but this doesn't help the patient who was taking Bextra[®] or another COX-2 inhibitor. Are we getting balanced reporting in the print media? Based on these examples that appeared in just a three-day period, I would say not. For the people in this room who are generating evidence, it is important to work very diligently to transfer knowledge that helps to inform patients about how to manage their health in "real time".

Why do the media report what they do report? Well, I want to share something quite disturbing with you. I attended a summit on drug review reform last January that was conducted by patient groups in partnership with Health

Canada. The folks from Health Canada people were there in force and this pleased us greatly because it improved dialogue between patient groups and regulators and policy makers. The keynote speaker at the summit was Andre Picard. It may appear that I am picking on him, but he just happened to accept the invitation. Actually, he provided the audience valuable insight into the media approach to healthcare stories and gave practical advice about how to get a story told in print. Among his recommendations: make sure your story is packaged and timed appropriately; know the story well so that its merits can be sold; keep the media informed about your group's events, challenges and achievements; and don't be afraid to use conflict as a way of dramatizing a story and increasing its appeal to editors. Now, I started work in the marketing and communications field, and it is interesting to note that these are actually product campaign principles. Frankly, this kind of framework for delivering scientific or other health information gives the public – and certainly patients – cause to wonder about the “news worthiness” of the news.

This leads us to a question that is very top-of-mind for my community and for me as a Canadian living with rheumatoid arthritis, “Are patient groups being shut out of the coverage on drug safety and drug access?” Regrettably, my answer would be “Yes”. You see, I belong to a group called the Best Medicines Coalition, a very large coalition comprising millions of Canadians living with life threatening illnesses and chronic diseases. I believe we are viewed by Health Canada as being credible spokespeople for many Canadians and active and responsible participants in shaping public involvement in federal decision-making processes. I was really pleased to hear about public involvement in decision-making in Dr. Peterson's presentation because this is an important way to ensure transparency in government decision-making. However, when the Best Medicines Coalition went to the editorial board of one of Canada's leading national daily newspapers we were told they would not meet with patient groups. Full stop. Then, staff at a well known and respected Ontario-based public relations firm was told by a high circulation provincial daily newspaper that it no longer printed letters from patient advocates because they are backed by pharmaceutical companies. I'm sorry, but this smacks of McCarthyism.

So what is the media really saying about drug innovation and patient safety? It is certainly my impression that, as a patient, I'm being portrayed as a weakling or scapegoat for industry, and that drug companies are profiteers who do not deliver innovation. In fact, the concept of innovation rarely creeps into the public media these days. And the drug regulatory body in Canada is characterized as either a hero or tyrant – which, I admit, is how I have viewed it from time to time. The bottom line is that articles in the print media are not about innovation and they are not about patient safety. Rather, they are about drama, and this is putting the public and patients at risk.

What Canadians are telling Health Canada about Drug Safety

Since the print media do not really give a sense of drug safety, let us move on to what Canadians are actually saying to Health Canada on this topic (see Further reading). Decima Research conducted a survey on behalf of Health Canada that is very enlightening. In March 2004, Health Canada published the results of this public opinion survey on key issues pertaining to post-marketing surveillance of marketed health products. Participants were asked to give their views and opinions on the effectiveness of Health Canada's methods of communicating health product safety information. Interviews were conducted with 1500 Canadian consumers and 551 health professionals, including physicians, pharmacists, nurses, dentists and naturopaths. Concerning perceptions of drug safety, 84% of consumers are most likely to believe that prescription drugs are safe (Box 1). This is a very high rating and it says that the great majority of people in this country believe these drugs are safe. 83% of health professionals felt the same way. Importantly for Health Canada, the survey found that 85% of consumers were confident in the system for protecting the safety of prescription drugs, and the figure was slightly higher for health professionals.

Participants in the survey were also asked about the importance of drug safety information. 85% of consumers said it was very important – which seems like a “no brainer”, considering the potential for serious adverse drug reactions. 90% of health professionals said that monitoring of drug safety is critically important to ensuring overall safety.

Box 1

Perceptions of Drug Safety		
opinion	consumer (%)*	health care professional (%)**
believe that prescription drugs are safe	84	83
have confidence in drug safety system	85	87
believe that drug safety is very important	85	90

* n = 356; ** n = 339

From: Public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada. Final report by Decima Research Inc to Health Canada, December, 2003.

Concerning sources of drug information, consumers relied heavily on pharmacists, but this is not a surprise to any of us in the room (Box 2). Interestingly, only 52% were satisfied with the information, so clearly there is room for improvement with this information source. Doctors were an important secondary source of information and, taking nothing away from the ability of pharmacists to inform, it can be argued that physicians came second as a source of information only because access to a physician is more restricted than to a pharmacist. Finally, the internet was an important resource for drug information, especially with respect to natural health products.

Box 2

Sources of information about prescription drugs relied on by consumers	
Source of Information	%*
pharmacist/pharmacy	84
doctor/physician/dentist	49
website/internet	24
medical reference books	6
TV/print media	2
friends/family member	2
product labeling	2
health food store	-
printed handouts from pharmacists	-
drug manufacturers	-
naturopath	-
other sources	3

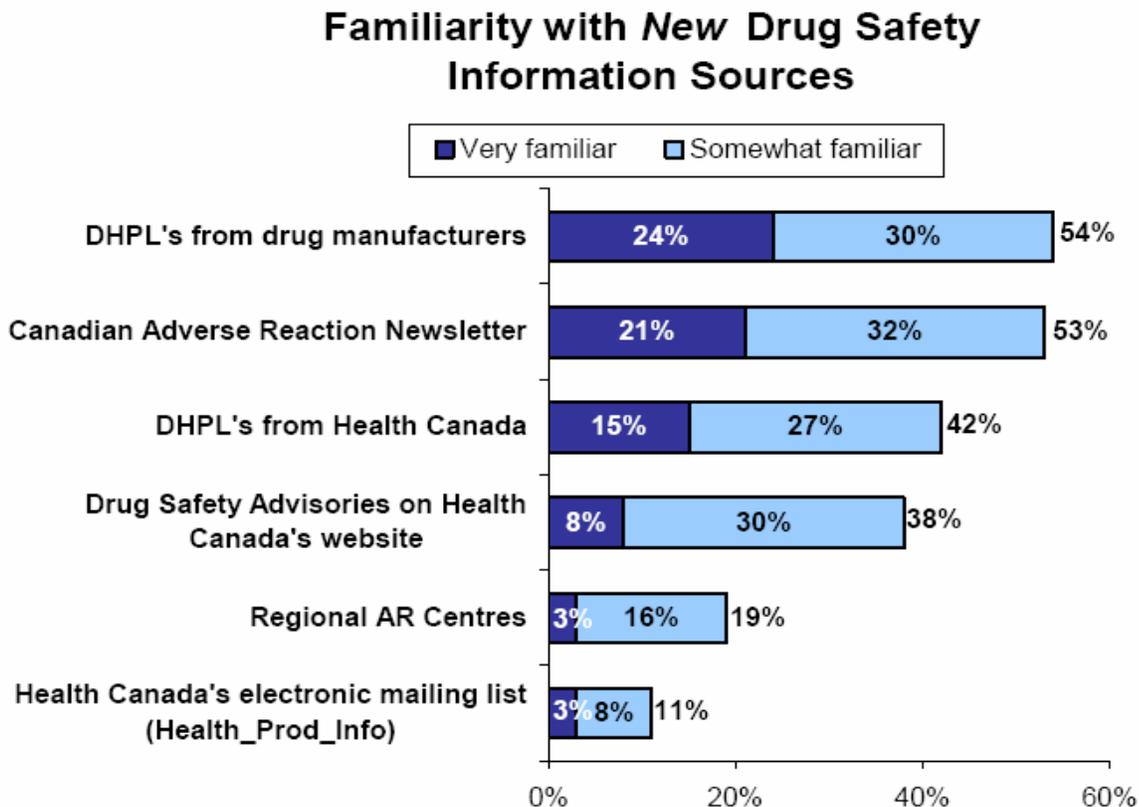
* n = 356

From: Public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada. Final report by Decima Research Inc to Health Canada, December, 2003.

The most important information coming out of this survey relates to new safety information. 62% of consumers reported that they are aware of public advisories published in the media. This suggests that the media is doing a good job of advising people. 31% said they were familiar with the Health Canada website, particularly with respect to new drug safety information. Less heartening are the findings that, among healthcare professionals, only 54% said they are very or somewhat familiar with the "Dear Health Professional" letters issued by industry and 53%

with the Canadian Adverse Reaction Newsletter (Figure 2). So, while all agree that this is an excellent tool, half of the health professionals are not using it. On the other hand, only 42% were familiar with Health Canada’s “Dear Health Care Professional” letters, suggesting that the drug industry is doing a slightly better job of reaching the desired audience than Health Canada. Drug safety advisories posted to the website were familiar to 38%, but only 19% of health professionals were aware that there are regional adverse reaction centres. These numbers are disturbing to patients and the general public.

FIG. 2



Another important finding concerns mandatory reporting of adverse drug reactions. 82% of consumers believe that health professionals should be required to report all adverse drug reactions brought to their attention, whereas only 14% thought that reporting should continue to be voluntary. Those opposed to mandatory reporting recognized that it would be an additional burden on health professionals or an unnecessary requirement. The feeling was that there is not enough time for practitioners to get the information needed just to function from day to day let alone adding to their list of duties, and that this activity really belongs in the regulatory domain. Interestingly, privacy was not considered an important issue to participants in this survey.

Moving Drug Innovation and Patient Safety Forward in Canada

First and foremost, Health Canada must focus on outreach to patients, health professionals and the public - and in that order - with **new** drug safety information. Health Canada, the pharmaceutical industry, health professionals and the voluntary health sector must do more to provide evidence-based information in lay language to the public and patients to ensure that they acquire the knowledge needed to be informed about their health status and to make treatment decisions in partnership with their physician. Why? Because according to Literacy Canada’s “Reading the Future” report from 1994, literacy is a significant issue in Canada.

- About 22% of adult Canadians 16 years and over fall into the lowest level of literacy. **Level 1** indicates that the individual may, for example, have difficulty identifying the correct amount of medicine to give to a child from the information on the package.
- 24-26% fall in the second lowest level. People who read at **Level 2** can deal only with material that is simple, clearly laid out and in which the tasks involved are not complex.
- 33% fall into **Level 3**. This level is considered to be the minimum desirable literacy threshold in many industrialized countries.
- Only 20% read at **Levels 4 and 5**, which indicates that they have the ability to integrate several sources of information or solve more complex problems.

To put this information into context, the recent Health Canada public advisory on Bextra[®] and other COX-2 inhibitors had a readability score of 27, well above the grade 12 level on the Flesch-Kincaid scale. To give a frame of reference, the Harvard Law Review achieves a readability score of 30. In other words, the Harvard Law Review is more readable than Health Canada's public advisories on drug safety information. In addition to providing accessible information on drug safety, Health Canada and the scientific community should develop an easy-to-use risk-benefit assessment tool for health professionals and their patients. This simply does not exist now. It could be argued that the wide dissemination of a very simple risk vs. benefit decision-making tool to the public would improve drug safety which in turn would encourage drug innovation. It is very important that public education on drug innovation and safety through social marketing campaigns should be undertaken. An excellent example of social marketing that actually captures the attention of the public was an Australian campaign to reduce the cost impact of back pain. We need to develop messages that reach out to the public and teach people about drug safety and about drug innovation. Finally, I think the media needs to better understand the need for drug innovation and the population served by that innovation. Based on the three articles presented, journalists do not understand this need. Journalists who write about health should learn about the different types and levels of safety information required for informing patients and the general public.

Conclusions

In summary, there is a big difference between the healthy public and the patient. Using too fine an innovation and safety filter at the public level will block the delivery of innovative drugs to those that need them the most, the sick and the dying. A one-size-fits-all health policy approach is not actually tracking with advances in science and as a result this approach will not meet the needs of Canadians. A national pharmaceutical strategy must include innovation or it has the potential to pose a greater safety risk to patients than potential adverse events. Finally, if you want to know what patients think about drug innovation and patient safety, ask them. They have the moral authority to speak on the topic and their voices, I would argue, are not being heard.

Further reading

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Antiretroviral Therapy 2005

Dr. Julio Montaner
Professor of Medicine and Chair, AIDS Research
Providence Health Care and University of British Columbia

The purpose of this presentation is to tell the story of HIV therapeutics in the last couple of decades, when knowledge went from nothing to what some people perceive as having found a solution. It will finish with the conclusion that the solution has not been found and furthermore that, if the pace of research does not continue, we are going to fall behind in a manner that is going to be severely adverse to the overall therapeutic effort.

To start, some basic questions: How does HIV lead to AIDS? What can be done to stop it? How can the risk/benefit of therapeutic efforts be optimized?

How does HIV lead to AIDS?

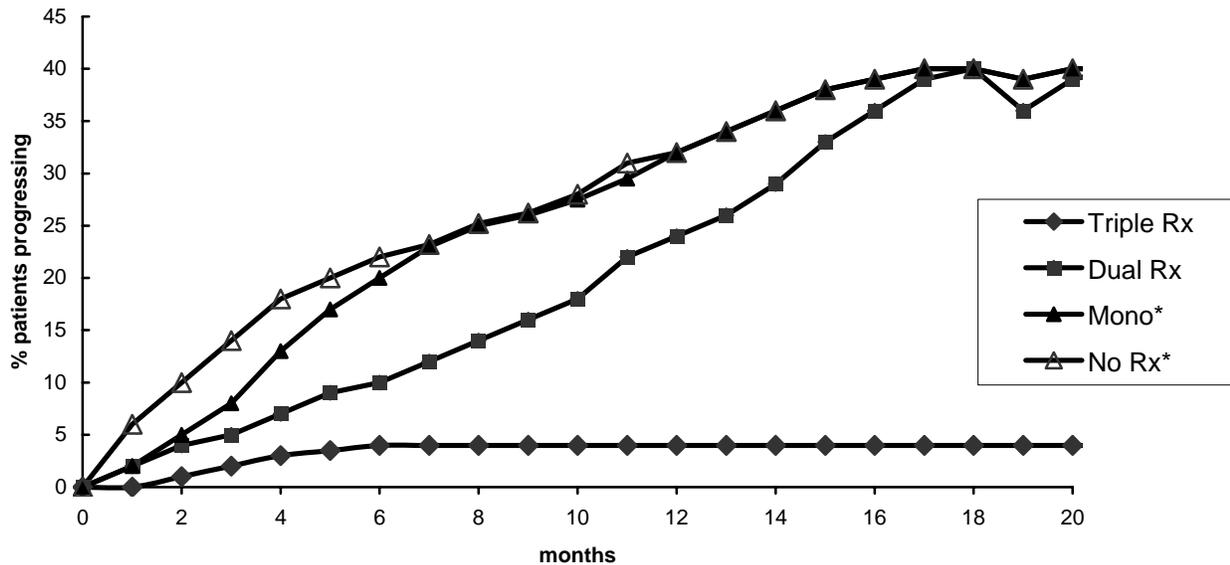
HIV is a retrovirus, and it is contracted basically through needle sharing or sex. The virus invades the system and immediately starts reproducing. Even before the immune system figures out what is going on, the virus is killing CD4 lymphocytes, which are mainly responsible for mounting an immune response against the virus. People infected with HIV lose the battle even before it starts. When CD4s are compromised immunity becomes sub-normal, but at first it is still clinically acceptable. However, it eventually drops to where patients develop an AIDS related complex of diseases, including opportunistic infections and cancers, and they die from these complications. The course between infection and eventual death from AIDS tends to be a decade or perhaps a decade and a half. For exceptional patients, about 1 to 5%, the disease course can be as short as 1 or 2 years. There are others who do extremely well, surviving even two decades without evidence of disease progression. This extreme variability of the illness adds to the complexities of deciding who should be treated, and when, and how. The truth is that untreated HIV leads to AIDS and this is 100% lethal unless the patient is lucky enough to be run over by a car.

Clinical manifestations of HIV include predominantly opportunistic infections and cancers. An example of such an infection is oral thrush, which would ordinarily be considered trivial but actually is the first sign, epidemiologically speaking, of disease progression. The disease can progress to esophageal candidiasis and later on to immune deficiency related conditions such as *Pneumocystis carinii* pneumonia. In the early days PCP was the commonest pneumonia affecting young gay men in North America and it was the fact that this infection caused severe disease and ultimately death that led to the discovery of the virus responsible. This infection can now be treated, and PCP today is a readily controllable condition. Another opportunistic infection, cerebral toxoplasmosis, can be quite devastating. Kaposi's Sarcoma, which used to be extremely infrequent, has become a stigma associated with HIV, for example in the west end here in Vancouver. There were many people walking around seriously disfigured with Kaposi sarcoma lesions on their faces, legs and arms. This has also now disappeared. These are just a few examples of things that can go wrong in people with HIV that is not appropriately treated. It bears emphasizing: all of these infections no longer exist in people who have treatment; unfortunately, this is only a minority of patients worldwide.

What can be done to stop HIV?

It is very simple. Figure 1 shows actual data that we published a few years ago showing disease progression to age of death in our cohort. The main reason the program has been doing reasonably well, in British Columbia at least, is because every single piece of data is systematically collected, and because information about drug use is centralized. As a result, we know what we are doing and what is happening and, for example, if a mistake is made, it is possible to make the right decision about changing patient management. The importance of systematic collection of data cannot be overemphasized. In a healthcare system that takes responsibility for the health of Canadians it is unacceptable not to collect the data.

FIG. 1 Proportion of patients progressing to AIDS/death depending on number of drugs used in treatment. Adapted from Hogg et al JAMA 1998 and CMAJ 1999



In the early days of treating HIV single drugs were used, because this was the only treatment available and because it worked to some extent. Using single drug treatment did not really give much of an advantage over no therapy, but for the patient it was worth treating in terms of short-term outcomes. However, after six months or so, the lines describing disease progression were superimposable. Based on this information, we rapidly moved on to more aggressive dual therapies. Dual nucleoside therapy put a bit of an inflection on the curve, displacing it toward the right, but it was not very satisfactory to see that the treatment and no treatment lines started to meet after a year or two.

It wasn't until 1994 that clinical trials on triple therapy were started, and it wasn't until 1996 that results showing a real difference in outcomes for people with HIV were reported at the Vancouver conference. As can be seen in Figure 1, the line for triple therapy inclines slightly for the first three or four months required for a treatment to take effect from an immunological standpoint, after which there is virtually no further disease progression. This is still the case today.

When the antiretroviral therapy programs were moved into the community and health outcomes were monitored, it was clearly shown that the risk of death in the province of British Columbia in the most at-risk patients (people with CD4 counts below 200) dropped very dramatically. Still today the rates of AIDS and AIDS death in the province of British Columbia are very low among patients who enter our drug treatment program. This is true even if patients who are not able to sustain the effort are included in the analysis, indicating that it doesn't take a lot of treatment to prevent bad outcomes, at least in the intermediate term. Similar trends have been reported from other countries, including the USA. There was a very dramatic drop between 1982 and 1994 and following the Vancouver conference in 1996 when triple therapy was first described. There was a very substantial decrease in mortality in the early stage as well.

What about a vaccine?

There are several vaccine candidates currently in clinical testing; however, efficacy is totally unknown and will take years to prove. The immunological context in Canada is different from that in, say Uganda, where 30% of the population is HIV infected, which means that the risk of children contracting HIV is much greater than in Vancouver. For the epidemiological situation here in Canada, not only drug efficacy is an important consideration

but safety is also paramount. Unfortunately the safety of an HIV vaccine will not be known for decades. If a vaccine were available today, infrastructure to implement an effective vaccine program worldwide would take several additional decades to develop. The problem is that the impact, epidemiologically speaking, will not be seen even by our grandchildren. It is therefore important to let the vaccine research continue, but at the same time the house is on fire and we have to continue to deal with this epidemic therapeutically over and above prevention.

How can we optimize the risk/benefit of HIV medications?

This is not a lecture about the toxicity of the antiretroviral medications. Nucleoside reverse transcriptase inhibitors (NRTIs) are well known to effect mitochondrial metabolism and can produce severe and potentially lethal toxicities, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have similar problems, including the inducement of inhibitors, severe dyslipidemia, and increased cardiovascular risk. The list goes on and on. The risks of current medication are very substantial, but of course the risks of HIV disease untreated is so much greater that it makes all of these risks acceptable. The key is to find a way to manage them.

At St. Paul's Hospital we have looked at the natural history of HIV. Some of the findings reported by John Mellors in *Annals of Internal Medicine* in 1997 were originally presented at the Vancouver conference. People with a low viral load in their blood have low rates of HIV progression and people who have higher viral loads have higher rates of progression. If patients are stratified by viral load and then by the CD4 count, the lower the CD4 count, the higher the risk of progression. Interestingly, people with CD4s less than 200 and a viral load of 30,000 have 100% progression at 1 year, a finding that is consistent with the data from our cohort studies. Because this data was generated at a time when antiretroviral therapy did not exist, we went back and challenged the assumption of the time. In 1996 when antiviral therapy was first developed, the thinking was that the immune system was suffering because the growing replication of HIV destroys CD4 lymphocytes, and we should therefore treat everybody before immune deficiencies develop. If our data on patients infected with HIV are reorganized based on the Mellors data, the only people who would not be treated would be those in the Mellors risk equation who have the lowest CD4 count and the highest viral load. Unfortunately, this is only about 5% of infected people, and about 90% of patients will be treated at any given time. Given the safety concerns about current medications and the difficulties associated with taking them, such as the development of resistance, it is not a surprise that caregivers were very uncomfortable with this scenario.

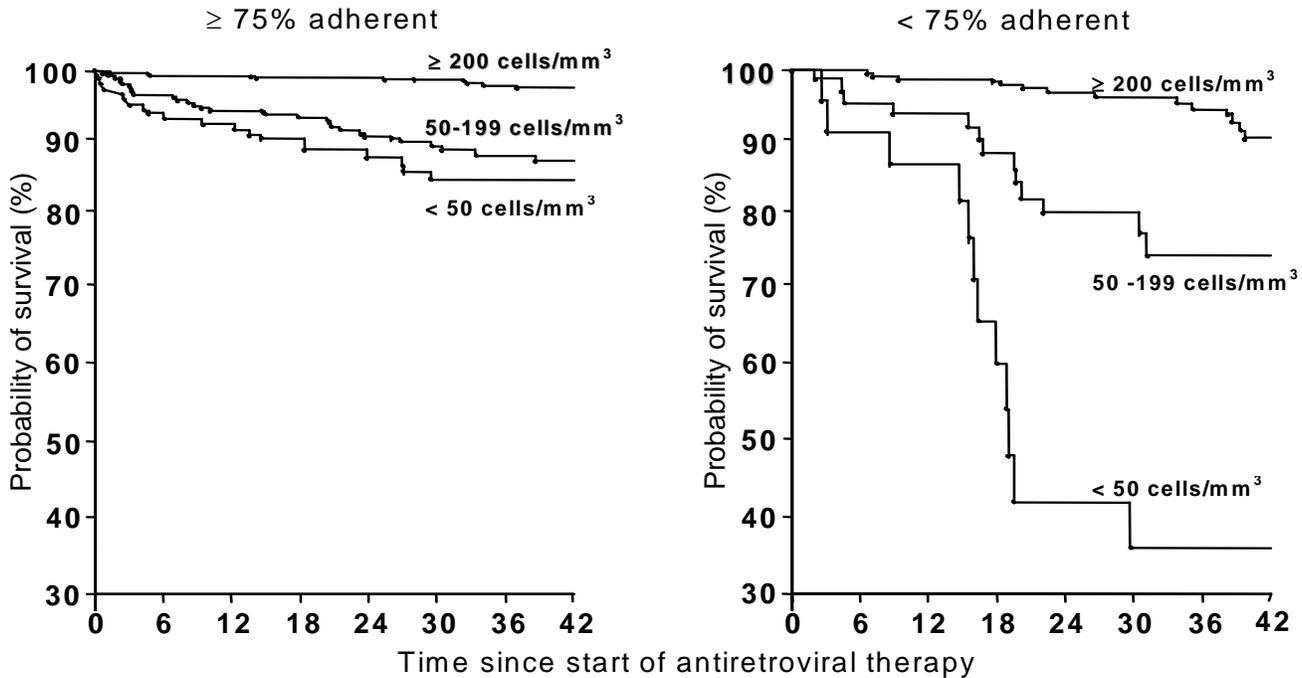
We looked into this further and verified what Mellors found. When all patients in the entire provincial database were stratified based on CD4 counts and viral load, it is clear that viral load had relatively little impact on survival outcomes. The reason for this is that potent antiviral drugs were being used. The effect of viral load, which was highly predictive of outcomes in the pre-antiretroviral therapy era, was erased with the advent of antiviral drugs and we were left with mortalities associated with very low or low CD4s. Patients who had more than 200 CD4s at the time treatment was started, regardless of any amount of viral load, if started on high antiretroviral therapy, had no evidence of disease progression. This gave a unique opportunity to rethink who should be treated. In fact, less than half of the patients originally treated actually required treatment.

This had a really dramatic impact on the goal, which is improve the outcomes of British Columbians infected with HIV, without unnecessarily exposing them to the risk of antiretroviral therapies. Of course, this also had a positive effect on the drug budget. By such monitoring we were able to gain insights that allowed us to optimize the risk/benefit ratio of our medications. These cohorts have now been followed for a number of years and recently published data clearly shows that the effect remains, that people who started treatment at a CD4 count of less than 200 do well. The reason, which was not known when the first patients were being treated, is that blocking viral replication over time in patients infected with HIV allows reconstitution of the immune system. High viral loads are transformed into undetectable viral loads as a result of the treatment and immunity rebounds.

We now have data that shows that even people with a CD4 count of less than 50 can reconstitute immune responses quite effectively. However, the problem is that they can also get sick and die during this process and we therefore do not recommend that people with CD4 counts below 50 delay treatment.

FIG. 2 The effect of degree of adherence to drug regimen on survival; from Wood E et al, Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? AIDS 2003;17:711-20 reproduced with permission.

Figure 2



Obviously, as Everett Koop said a long time ago, these drugs are not going to work if patients don't take them. To examine this issue, data on mortality, morbidity, adherence, and other biological and socioeconomic parameters were collected and this information demonstrated quite convincingly that even people with very low CD4s, less than 50, who adhere to their drug regimen do dramatically better than people who are incompletely adherent (Figure 2). This is not to suggest that adherence is not a very complex variable that relates to physician/patient interaction, drug tolerability, safety, as well as other issues, and is not simply the fact that some patients are good and others bad. There are also good and bad doctors and good and bad drugs.

Current recommendations

We currently recommend that all symptomatic patients be treated and, for asymptomatic patients, further research has resulted in the recommendation that treatment be initiated before the CD4 count is 200 or before the CD4 is reduced by 15%, regardless of HIV RNA level. Over and above that, treatment should be started only when the patient is ready to commit. The medical community has the responsibility to work towards increasing that commitment.

Box 1

NRTI component
lamivudine or emtricitabin + zidovudine or tenofovir or didanosine + emtricitabine <u>alternative:</u> abacavir + lamivudine didanosine + lamivudine didanosine + tenofovir stavudine + lamivudine zidovudine + abacavir
NNRTI component
efavirenz (or nevirapine in selected patients)
Protease inhibitor component
lopinavir/ritonavir saquinavir/ritonavir indinavir/ritonavir atazanavir/ritonavir <u>alternative:</u> nevirapine fosamprenavir/ritonavir atazanavir

To discuss all of the specific drugs would take the rest of the day. But it is useful to highlight the International AIDS Society/USA 2004 guidelines for antiretroviral therapy on which we collaborated (Box 1). The initial treatment for HIV today is fairly simple, but it needs to be emphasized that these guidelines change significantly about every two years – the field is in a state of very rapid evolution.

We are constantly being asked what to use as preferred treatment and now there finally is data that shows that really it matters less which treatment is used than how it is used. About a month ago John Bartlett and his colleagues presented a comprehensive compilation of 49 clinical trials conducted recently showing that the level of effectiveness of the two regimens that we currently recommend, boosted protease inhibitors (PIs) and NNRTIs in triple therapy, are very comparable (abstract 586, Conference on Retroviruses and Opportunistic Infections, 2005). Triple nucleosides or non-boosted PI regimens are inferior and current guidelines do not recommend them. CD4 gains are comparable for all regimens and it boils down to the issue of optimizing the regimen for the individual patient.

What have been improving over the last several years are overall outcomes of clinical trials. Since 1996, when the rate of failures in the first year was about 4000 subjects for five different cohorts in Europe and Canada, the rate of failure has been dropping quite significantly. It must be pointed out that, although this is true within the first 24 months of treatment, 25% of patients subsequently fail, so this is a disease that will have to be treated effectively over the long term. We need to pursue aggressive therapy alternatives.

The FDA has now approved a number of fixed dose combination antiretroviral therapies and this helps because it simplifies the regimen, but they also increase the risk when patients forget or misuse the medications, thereby exposing

the virus to less than optimal drug levels. However, it is hoped that there will be more and more fixed dose combination drug treatment available. These do not necessarily compromise regimen flexibility and should increase the ability of patients to take drugs as prescribed.

The need for new antiretroviral therapies

One may wonder why new drugs for antiretroviral therapy are needed if current outcomes are so promising. The reason is that simpler regimens are needed. HIV/AIDS is a condition that requires greater than 95% adherence at all times otherwise resistance supervenes, and people who develop resistance have a significantly increased risk of death. We need simpler regimens, safer drugs and better tolerated drugs so that people can take them on a long-term basis without difficulties. There is a very important issue with drug interactions. Almost all of the drugs current used are very powerful cytochrome P450 inhibitors, and very little is understood of what this will do to patients in the long haul. For this reason patients must be monitored very closely for drug interactions and toxicity. Drug resistance is estimated broadly to be about 5% a year in patients treated for HIV. This means that the effectiveness

of first line drugs is very rapidly being compromised. More and better drugs are needed and quickly. But at the same time a sharp eye must be kept on their safety, particularly in the long term. This is an area where much is unknown and where the process is often very poorly monitored. At the British Columbia Centre for Excellence in HIV/AIDS we have an initiative concerning long term safety but the sample size that is required to show, for example, that cardiovascular risk is changed in patients treated with antiretroviral therapy, is somewhere in the range of 20,000 to 30,000. Hopefully British Columbia will never have this number. Incentives at the federal level to collaborate with our colleagues in the rest of the country are needed so that cohorts of patients can be combined to allow detection of toxicities before they become a serious concern. There is also the need for a process to monitor long term safety.

The Canadian Therapeutics Product Directorate has always taken longer to give regulatory approval for antiretroviral drugs than the US Food and Drug Administration. This is of concern since the TPD has never made a decision that differed substantially from the FDA. Time for approval is measured not just in days but in months and years. In my view this is unacceptable. If there were some divergence in the ultimate decision, this would be more tolerable. However, the fact that it is taking twice or three times as long to rule on these issues is putting the health of patients in jeopardy at a time when there is a need for all the help we can get to access medications promptly.

Summary

HIV is the cause of AIDS, a statement that needs to be repeated because from time to time the press gets it wrong. Failing to treat HIV is a 100% guarantee that it will progress to AIDS and eventual death. Treatments are very effective, but not perfect. There will not be vaccine in our lifetime and therefore the strategy for the treatment of people with HIV needs to be planned very carefully. We need to optimize the risk, including costs as well as in terms of risk/benefit and cost/benefit ratios, and the only way to do this is with a comprehensive surveillance mechanism. Such a system of active surveillance throughout Canada is unfortunately not yet in place.

Further reading

1. Wood E, Hogg RS, Harrigan PR, Montaner JSG. When to initiate antiretroviral therapy in HIV-1-infected adults: a review for clinicians and patients. *Lancet Infect Dis* 2005;5:407-14.
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3. Wood E, Hogg RS, Yip B, Harrigan PR et al. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 0.200 to 0.350 x 10⁹ cells/L. *Ann Intern Med* 2003;139:810-6.

Drug Safety: The Oncology Perspective

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Introduction

I will give a general overview of how the evaluation of drug treatment for malignant disease is approached and specifically how this differs from other sub-specialties. Many drugs used to treat cancer can have serious toxicity, and concerns about drug safety and evaluation of risk/benefit are very important parts of every therapeutic decision. I will talk about strategies used to alter the risk/benefit ratio, some of which will also be discussed at the symposium this afternoon about pharmacogenetics.

Like all drugs, those used in oncology have adverse effects, some of them quite profound. Because of the nature of the treatments, many of these toxicities are expected, including acute toxicities such as bone marrow suppression and nausea and vomiting, which are usually manageable. There are also chronic cumulative toxicities that are drug specific and generally not treatable. Now that larger numbers of patients are being cured, more longer term effects are being seen and these must also be factored into decisions. The greater challenge is with the toxicities that are less predictable. Some are related to treatment but they can also be related to the disease itself, and it may be difficult to distinguish the cause before data from comparative trials become available. Generally in oncology drug safety is evaluated in the context of the disease being treated. Clearly, when treating a fatal disease a much higher degree of toxicity is accepted than when treating, for example, a GI motility disorder. Also, treating people who will inevitably die of their disease is very different from treating patients who potentially might survive.

Development of Drugs for Oncology

There are a few points to make in terms of drug discovery and development in cancer treatment. In general, the introduction of new drugs does not occur uniformly across disciplines. Particularly in the 1980s, very few new oncology drugs were introduced into the clinic, whereas many new drugs became available for cardiovascular and gastrointestinal conditions. This has changed, and now oncology is the leading disease for which there are new drugs. Fortunately these drugs are a significant improvement, partly because they are more specific for cancer in much the same way that anti-infectives target features that are specific to the infective agent as opposed to the host. Newer anti-cancer drugs are similarly targeted against features of the malignant phenotype. As a result, these drugs have much less toxicity, a fact that has actually changed the way drugs are developed. Traditionally in cancer treatment the dose of the drug is increased until the patient cannot tolerate it, assuming that this will result in the best dose. However, some of the newer drugs are much less toxic and escalating the dose to the point of intolerance may not be the best way to determine the optimal dose.

For oncologists phase 3 trials remain fundamental to developing new drugs and the main reason for this is that, with few exceptions, advances in oncology occur in small steps, and it is very rare to have such a marked improvement in therapy that a randomized trial is not required.

From the perspective of someone who has been working in this field for 15 years it is quite clear that the administrative and regulatory work load associated with new drug trials has increased substantively. However, it is less clear that this has been associated with a parallel increase in patient safety. A final point about the development of drugs for oncology is that, as has occurred in HIV therapy, combination therapy is clearly the way to go. Many of the interesting new drugs which are not yet approved have been developed by different pharmaceutical companies. While pre-clinical evidence suggests that the maximum effect occurs when used in combination with other drugs, trying to do clinical trials with unapproved drugs from two or more different companies is almost

impossible. One initiative that has been positive in this regard is in the US, where the FDA has obtained agreements from some companies to allow the National Cancer Institute to develop specific combinations of investigational drugs. The regulatory environment for drugs in oncology has also changed because the FDA, recognizing the unmet needs, has lowered the bar for drug approval. One approach has been giving approvals that are provisional upon the collection of subsequent data. For example, as Dr. Peterson mentioned, provisional licensing was given for gefitinib (Iressa®) in lung cancer, a drug that now may well be withdrawn from the market based on the additional data that has become available.

Another issue is that paying for these new drugs will be one of the major challenges in health care in the next decade. They will be expensive, in the range of \$50,000 per year, and they will be effective for common cancers, such as colon cancer, so that the total cost to the Canadian health care system is going to be substantial.

Many of the examples I will be using relate to colorectal cancer. There have been major improvements in therapy for this disease: whereas in 1995 there was really only one drug available, in 2005 we have many different drugs and classes of agents (Table 1).

TABLE 1 Drugs available to treat colorectal cancer – 1995 and 2005

1995	2005
thymidylate synthase inhibitors <ul style="list-style-type: none"> • 5-FU + leucovorin • 5-FU infusion(s) 	thymidylate synthase inhibitors <ul style="list-style-type: none"> • 5-FU + leucovorin • 5-FU infusion(s) • capecitabine (Xeloda®)
	topoisomerase inhibitors <ul style="list-style-type: none"> • irinotecan (Camptosar®)
	platinating agents <ul style="list-style-type: none"> • oxaliplatin*
	biological agents <ul style="list-style-type: none"> • cetuximab (Erbitux®)* • bevacizumab (Avastin®)*

* available in US; not yet approved in Canada

However, in oncology we have the same problem as pointed out by Dr. Montaner concerning drugs for HIV, three of the newer drugs listed have been approved for use in the US and in the EC for more than a year, but do not yet have a Notice of Compliance in Canada. This is partially attributable to the fact that, from a global point of view, Canada is a relatively small market and industry will file initially in the larger markets. But regardless of the causes there are concerns about access for Canadians to some of the new innovative products.

Cancer Treatment in 2005

When most people think of cancer treatment they think of unpleasant effects such as losing hair and vomiting. These occur most commonly with ‘traditional’ cytotoxic chemotherapies and many of the principles I will be talking about concern such effects. The newer biological or targeted therapies such as the anti-vascular drugs have generally less toxicity, although as they are used more commonly we are discovering they are not free of toxicity, it

is just that rates are lower. We also commonly use supportive therapies such as anti-nauseants or steroids as a component of cancer treatment, often to deal with the toxicity of the treatment. When treating metastatic cancer in patients who will inevitably die of the disease, there is less concern about drug safety issues, particularly longer term toxicity, if the overall balance of effect is favourable. However, when considering potentially curable disease the longer term issues become more important. It has recently been seen that when using drugs such as tamoxifen, which is considered extremely safe for the treatment of established cancers, as a cancer prevention agent, relatively infrequent but more serious toxicities become more important.

Principles of Chemotherapy

Historically, chemotherapy has involved the use of some very unpleasant compounds. Chemotherapy started with nitrogen mustard, a derivative of sulfur mustard gas which was used with very unpleasant consequences in the First World War. We are currently involved with a clinical trial of ricin, one of the most toxic biological agents, as a cancer treatment, and another new treatment is arsenic trioxide for hematologic malignancies. What some people see as challenges, oncologists consider opportunities and clearly dealing with toxicity has always been very important for oncologists.

The use of allogeneic bone marrow transplantation to treat acute leukemia can be considered the ultimate high risk/high benefit situation. Acute leukemia is almost invariably fatal, usually relatively rapidly. One potential treatment is allogeneic bone marrow transplantation, which involves giving bone marrow from a healthy matched donor to the patient. The risks of this procedure are quite substantial with treatment related mortalities around 20%. Yet, despite this, a pivotal study reported some years ago in the *New England Journal of Medicine* demonstrated the overall benefit of this approach. While in the short term more people die due to treatment complications, in the longer term more are cured of an otherwise fatal disease. In other words, a drug or treatment that will kill 20% of patients may be still be considered acceptable when viewed in the context of longer term survival.

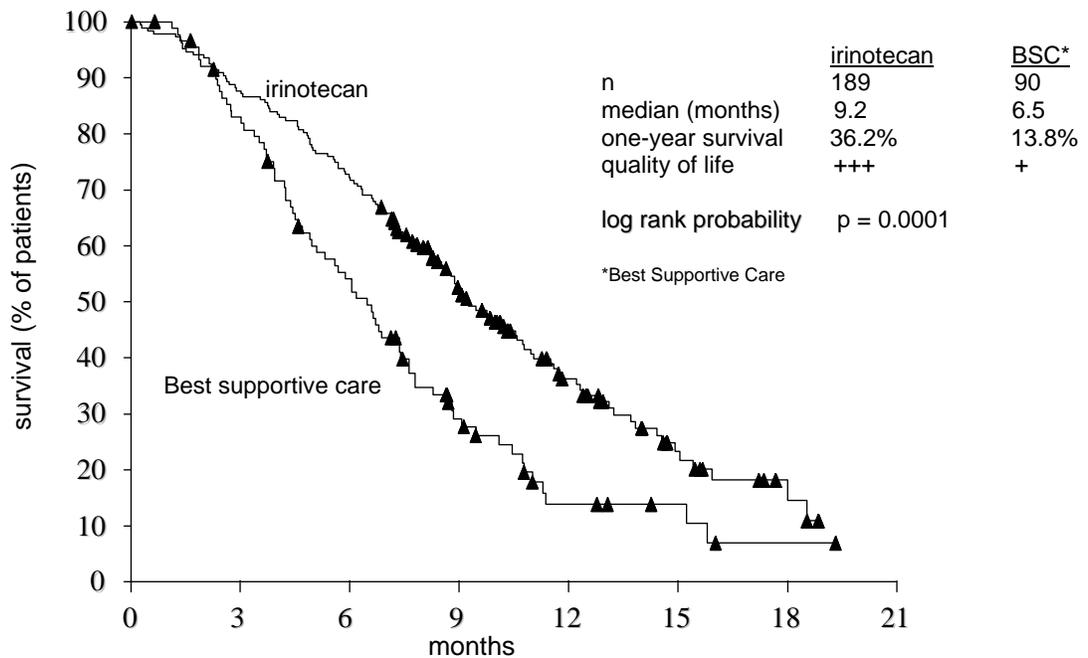
The Quality of Life and Patient Safety in the Treatment of Colon Cancer

One can also look at quality of life as well as survival when evaluating the trade-off between risk and benefit. Irinotecan, a topoisomerase 1 inhibitor with activity against colorectal cancer, is fairly toxic, in particular causing diarrhea, nausea and fatigue. Irinotecan was compared against best supportive care in patients with very advanced colon cancer in a study done in England (Figure 1). This trial showed that patients who received this drug not only lived longer but they also had an improved quality of life compared to those who did not receive treatment.

This is frequently seen in cancer treatment, where even when using drugs with significant toxicity, the unpleasant effects of the cancers are worse than the toxicity of most treatments. If the cancer can be improved, the patient will usually be better.

As an example of how adverse drug reaction assessment works in the real world of drug therapy for cancer let us examine the subsequent development of irinotecan in colorectal cancer. Once irinotecan was introduced based on data from Cunningham's study, the next logical step was to combine it with what was then the standard therapy in patients with untreated metastatic disease (5-FU). Two randomized studies showed that the combination of irinotecan with 5FU resulted in relatively modest benefits: median survival increased by several months. In terms of safety there was more diarrhea and fatigue but, because the patients lived a little longer, the combination became the standard of care. Chemotherapy in colon cancer is used not just in patients who have disease that has spread (and is incurable), but also in patients who have had the disease removed surgically and who are at risk of the cancer coming back. If the cancer recurs the patient will die of the disease. So, treatment after surgery is given to prevent recurrence, and it has previously been shown that more patients receiving 5-FU chemotherapy after surgery remain free of progression and are cured.

FIG. 1 Irinotecan vs. best supportive care with metastatic colon cancer; reproduced with permission.



Thus, the next step with the combination of irinotecan and 5FU was to find out if it will improve the cure rate beyond what would be achieved with 5FU alone. To explore this possibility two large trials began. The first compared leucovorin to alternate regimens in advanced disease. The second compared it to 5FU after surgical resection in the population of patients that was about 50-60% cured by surgery alone, in which the objective was to improve on this rate. It can be difficult to assess the outcomes of such trials while they are still ongoing because many patients die from the disease and related causes. The Data Safety Board that was reviewing data from these trials had set up a system for identifying the cause of early death. The Board determined that patients treated with the irinotecan plus 5FU regimen in one of the studies had an early death rate of 4.8%. This appeared to be high: generally in oncology trials treatment related mortality of about 1-2% is expected. The second study also showed excess deaths, although at a somewhat lower rate of 2.2%. Since these treatments were used in a group of patients who were potentially cured, this rate of early deaths was unacceptable, and the trials were closed.

An independent review panel was convened to try to attribute cause of death in these trials and this turned out to be a challenge. Sorting out which deaths were treatment-related, which were totally unrelated, and which were contributed to by treatment was very difficult. Consider, for example, a patient who dies of a cardiovascular event: did dehydration caused by drug related diarrhea play a contributing role? It is clear that real time monitoring of very severe toxicities does help to identify problems early in trials. In this particular example, the regimen has now been abandoned in favour of safer ways of giving these drugs, or of using other drugs altogether.

Tamoxifen for Breast Cancer

Continuing on the issue of patient safety but changing the patient population, hormonal treatment for breast cancer is generally considered extremely safe. It was shown in a variety of trials that, when hormones were used to treat an established breast cancer, there was some reduction in the incidence of new breast cancers occurring in the other breast. This led to the assessment of what were considered very safe drugs for primary cancer prevention. Tamoxifen was the lead compound assessed in very large clinical trials to study breast cancer prevention in women who had never had the disease, and in fact there was a 46% reduction in the incidence of breast cancer. Breast cancer is a serious illness and this is an important reduction. However, when we get into trials in which tens of

thousands of women are enrolled new issues emerge. These women were also found to have a higher incidence of uterine cancer and the uterine cancer was often fatal. They also had a higher incidence of thromboembolic disease and osteoporosis. As a result, in spite of the fact that this drug has been approved by the FDA for prevention of breast cancer, it is rarely used because many view the risk/benefit ratio as marginal or unfavourable.

Tracking Adverse Reactions in Oncology Trials

I would like to make some personal comments about the evaluation of adverse drug reactions in oncology clinical trials. The chair of our ethics board informs me that the volume of reports generated in oncology trials tends to be the highest of any type of therapeutic trial. As previously stated, attribution of events is often difficult: only at the time of the final report, when population A can be directly compared to population B, is there a reasonable understanding of attribution. Every day there is a thick folder on my desk containing about 50 serious adverse event documents from the current clinical trials. I sign at the bottom of each report and then they are filed. As more and more adverse event reports are generated, just dealing with this aspect of conducting clinical trials becomes a challenge. If the threshold for reporting is increased the danger is that really important events will be missed in the tsunami of reports that are either trivial, or probably attributable to the disease rather than the drug. In addition to this, nobody appears to be paying attention at a higher level to collecting, collating, and summarizing this data. Our research advisory boards are just not able to do this because of the sheer volume of these reports.

Patient Perspective of Drug Safety in Oncology

Cheryl Koehn has addressed the issue of patient perspective. Dealing with cancer patients one learns that there are very different views about what sort of risks people are prepared to take and how they interpret the value of therapy. For this reason, I am not keen on living wills, because people often will say, "I would never take chemotherapy, it's too toxic". However, if they develop cancer their perspective may change completely. It is very important to discuss the risks of therapy with the patient so that they can consider this information when making decisions about whether or not to undergo treatment. However, what is defined as acceptable or unacceptable risks by people who do not have these diseases may be very different from what actual patients may think.

Along the same line, in my opinion the informed consent has now become a useless tool for informing patients about the risks of therapy in clinical trials. Cheryl Koehn spoke about the fact that the readability of Health Canada warnings is less than that of the Harvard Law Review. The readability of most informed consents now is much less than that of Health Canada warnings. Most are more than 10 pages, completely unreadable and, much like mortgages, they go on and on. Ethics committees tend to become very involved with the minutia of what's in the informed consent. Should 20-30% be considered a moderate risk?

The investigators and ethics committees argue back and forth about the wording of page seven of the consent form and the investigators invariably concede to the ethics board because the trial has to be approved. Nobody is looking at the big picture and asking:

"Is giving the patient a 15 page consent form with every conceivable toxicity listed on it really providing them useful information in terms of making decisions?"

Strategies for Reducing Toxicity of Drugs for Cancer

Table 2 summarizes some strategies for reducing toxicity in oncology. The principle that the higher the dose the better is changing and lower doses are being tested, particularly in older patients, to see if the same effect can be achieved. In addition, for most of the acute toxicities, pharmacological ways of managing have been developed instead of abandoning treatment. Also, structures of effective but toxic drugs are being modified to find out if analogues have the same benefits, but reduced side effects (Table 3).

TABLE 2 Improving drug safety by pharmacological manipulation

Side effect	Treatment
nausea and vomiting	<ul style="list-style-type: none"> • 5-HT3 antagonists • steroids
bone marrow suppression	<ul style="list-style-type: none"> • recombinant human granulocyte colony stimulating factor • erythropoietin
diarrhea	<ul style="list-style-type: none"> • loperamide
thromboembolic events	<ul style="list-style-type: none"> • warfarin • low molecular weight heparin
cystitis	<ul style="list-style-type: none"> • mesna
nephrotoxicity	<ul style="list-style-type: none"> • hydration • mannitol

TABLE 3 Improving drug safety by developing analogues

Old drug	Analogue
cisplatin	<ul style="list-style-type: none"> • carboplatin • oxaliplatin
doxorubicin	<ul style="list-style-type: none"> • epirubicin • mitoxantrone
camptothecin	<ul style="list-style-type: none"> • irinotecan • topotecan

Pharmacogenetics

I will conclude with some comments about pharmacogenetics. When a patient with colon cancer is treated with a drug there is probably a 50% chance that the drug will help and a 25% chance that there will be severe toxicity. The challenge in oncology is to find ways of changing those figures to more favourable rates. It appears that looking at the pharmacogenetics of both the host and the tumour may assist in doing that. For example, for the commonly used drug, 5-FU, if the tumour over-expresses thymidylate synthase, the target of this drug, it is very unlikely that it will be effective. The future in oncology will be in looking at both the host and the tumours to individualize drug therapy and using that as a strategy to make the drugs safer.

Summary

For cancer treatment, adverse drug events and drug toxicity are accepted as part of treatment. These are sorted out mainly by conducting randomized trials and by looking at strategies to improve drug safety both from a genetic point of view and by altering doses and schedules.

Further reading

1. Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med* 1998;339:1649-56.
2. Cunningham D, Pyrhonen S, James RD, Punt CJ et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413-8.
3. Saltz LB, John V, Cox JV, Blanke C et al for the Irinotecan Study Group. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905-14.

Commentary by a Regulator

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I want to thank the organizers for bringing together the range of expertise of those attending this symposium. Certainly I have learned a great deal from the presentations. I will be brief in my comments because I think there is a desire to have a discussion about what was heard.

Let me reflect on a few things that were said. First of all, I think it is absolutely critical to have the types of people in this room – researchers, investigators, academics, students, practitioners, patients, Health Canada, provincial representatives, and the industry – involved in the kind of dialogue that we need in Canada around the issues of drug innovation and patient safety. I'm not sure whether media people are present but I was quite taken by Cheryl Koehn's remarks about their role and I know they will be present when the Minister comes, which speaks for itself.

Clearly, a lot of information was presented here and the challenge of translating that knowledge into good public policy is at the heart of what I see as my responsibility. The mandate of Health Canada is to help Canadians maintain and improve their health. I know that everybody shares a common mission in terms of improving health outcomes for Canadians and this is certainly what we have heard today. I was disturbed by Dr. Montaner's remarks with regards to the performance of the Therapeutic Products Directorate, not because I don't agree with him but because such tremendous improvements have been made in that area. Without going into detail about how we are doing in terms of performance, I think the challenge is not to think about access to drugs in Canada in isolation from the rest of the system. For example, access includes product development.

Stuart MacLeod talked this morning about research and development that really focuses on public health needs and this has also been mentioned, at least implicitly, by a number of other speakers. Access certainly includes the approval and availability of products on the market. Dr. Moride was talking about the very blunt instruments that the regulator has, and I would agree that we should not be deciding only whether a product is on the market or off the market, but should rather be considering the possibilities between these extremes.

Let me turn to submission of drugs for approval and their subsequent marketing by the pharmaceutical industry. At Health Canada we have been tracking times submissions are received in Canada in comparison to the US FDA. It turns out that this quite often occurs much later in Canada, by which time of course there are more adverse events as well as other data that then must be reviewed. As well, there are differences between the date on which a product is approved and the time of bringing a product to market. Sometimes the gap is a year or even more. Sometimes we approve a product that is never brought to the Canadian market. I put the challenge of coming up with an equitable way of comparing time to market between countries that takes such differences into account.

There are a number of other factors that influence drug marketing in Canada. The formulary systems within the provinces obviously have an important effect, but there are also other initiatives at the federal, provincial and territorial levels. However, the machinery can be slow and cumbersome, so that the real challenge is for us to work together in a different kind of relationship to move forward on some of these issues.

Public confidence in Health Canada about the products we regulate is critical and I would argue that that confidence is shaped by all of us in this room. Cheryl Koehn gave some data about the confidence that Canadians have in Health Canada as a regulator, but also important is the confidence Canadians have in all of the organizations throughout the system that influence access to therapies. Certainly, concerning recent events about certain products, I learned something new, and that is that Canadians believe that Health Canada already had information that it should have acted on. Or else they believe that Health Canada should have had information that

it should have acted on. There are some challenges here in terms of who is accountable, who has the information, who should act on the information and how information can be better shared.

Cheryl Koehn also talked about conundrums and others have talked about changing paradigms. “Hero and tyrant” as a definition for the regulator is not one I mind actually: we are called far worse everyday so these are epithets we can live with.

A book by Malcolm Sparrow published recently (The Regulatory Craft: Controlling Risks, Solving Problems, and Managing Compliance) discusses challenges faced by the regulator and I will cite some pieces of advice that appear to be conundrums or paradoxes. He says: “be less intrusive – but more effective; be kinder and gentler – but don’t let the bastards get away with anything; process things quicker – and be more careful next time; be more responsive to the regulated community – but do not be captured by industry”. This advice gives an idea of the world we live in as the regulator.

I also liked Craig Hartford’s “safe and sorry”. I was reading an article the other day that came from the Kennedy School of Business at Harvard which suggests changing the paradigm from “speaking truth to power” to “finding truth for power” and I think that is one of our challenges as well.

I am very much looking forward to the discussion and debate about what has been presented. Certainly, I heard a shared commitment in the room to look for data, to seek evidence, and to act on information throughout the entire system. If we don’t do these things, what we now are proud of in terms of evidence-based decision-making may well become decision-based evidence-making.

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