



**HOUSE OF COMMONS
CANADA**

**POST-MARKET SURVEILLANCE
OF PHARMACEUTICALS**

**Report of the Standing Committee on
Health**

**Joy Smith, MP
Chair**

JUNE 2008

39th PARLIAMENT, 2nd SESSION

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has the honour to present its

SEVENTH REPORT

Pursuant to its mandate under Standing Order 108(2), the Committee has studied the federal government's role in the post-market surveillance of pharmaceutical products, prescription and non-prescription and presents its findings and recommendations.

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POST-MARKET SURVEILLANCE OF PHARMACEUTICALS

SECTION ONE: BACKGROUND

In January 2008, the Standing Committee on Health commenced a study on the federal government's role in the post-market surveillance of prescription and non-prescription pharmaceutical products.. At that time, the Committee understood post-market surveillance to encompass the monitoring of safety, efficacy and quality of products after they are approved, marketed and disseminated to the general Canadian population. While these factors are assessed in the pre-market phase, additional information becomes available after a product goes to market and is utilized by a wide population.

Health Canada's role as the federal regulator of pharmaceuticals under the *Food and Drugs Act* was the primary focus of the study. On this aspect, the Committee looked at the department's post-market regulatory authority, its capacity to monitor activities, and its overall ability to carry out investigations and compliance. It also examined departmental interactions with manufactures, health professionals, and consumer/patient groups on various post-market elements including adverse reaction reporting, direct-to-consumer advertising and general information sharing.

In addition, the Committee explored the federal government's broader role in post-market surveillance activities. It heard about the contribution to data collection and research on drug utilization, safety and effectiveness through initiatives such as the federal/provincial/territorial (F/P/T) National Pharmaceuticals Strategy (NPS) and the National Prescription Drug Utilization Information System and organizations such as the Canadian Institute for Health Information (CIHI), the Canadian Patient Safety Institute (CPSI), and the Canadian Institutes of Health Research (CIHR).

SECTION TWO: HEALTH CANADA'S PROPOSED NEW APPROACH

Over the course of the study, the Committee heard evidence from Health Canada officials and other witnesses about a new proposed approach to post-market surveillance being developed under its federal regulatory authority. Health Canada informed the Committee that, through changes to the *Food and Drugs Act*, it was seeking authority to implement a life-cycle approach to regulating pharmaceutical products. According to their testimony, the legislative intent would be to continuously assess a product's risks and benefits, through all stages of development and use, that is, both before and after it reached the market.

In the post-market phase, the proposed legislation would put conditions on the licence to market, increase fines and penalties, and provide the power to remove unsafe health products from the market. In cooperation with the provinces and territories, the legislation would make it mandatory for hospitals to report on serious adverse drug reactions. It would also support greater public involvement in regulatory decision-making by increasing openness and transparency of Health Canada's regulatory activities.

On 8 April 2008, as the Committee was in its final stages of public hearings on this study, the Minister of Health introduced Bill C-51, *An Act to amend the Food and Drugs Act* in the House of Commons. As of the end of May 2008, Bill C-51 remained at the First Reading stage in the House and thus had not been referred to the Health Committee for detailed consideration as part of this post-market study.

While not specific to the clauses of Bill C-51, much of the testimony did refer to proposals relevant to the pending legislation. Consequently, the following document provides evidence from witnesses about the current state of post-market activities at the federal level, reflects their testimony about the implications of future proposals, and where relevant, notes specific elements of Bill C-51.

A. Risk, Benefit and Context for Use

Health Canada stressed that its current and proposed approach to post-market surveillance is based on sound risk management principles that require the risk of a pharmaceutical product to be weighed against its benefits. Thus, since most of the 22,000 pharmaceutical products available in Canada involve a risk, the degree of risk is assessed in relation to the benefits of its use such as the number of lives saved or the number of years of increased life expectancy. For example, it was noted that although the blood thinner called Coumadin has a known risk of 1% per year for serious gastrointestinal bleeding, the significant numbers of strokes prevented each year makes its use a good decision for population-based health outcomes.

Witnesses generally agreed that the context for the use of a pharmaceutical product would affect the degree of risk that was acceptable. However, they noted that acceptable risk in one situation may not be appropriate for another case. For example, the use of a non-steroidal anti-inflammatory drug to relieve debilitating pain for certain people suffering from rheumatoid arthritis might permit the acceptance of liver problems at a later stage but not the use of the same drug for the treatment of tennis elbow. In other cases, a greater degree of risk might be acceptable depending on factors such as the type of disease, whether the drug constituted a therapeutic breakthrough, or whether the patients had other available options

Witnesses felt that pharmaceutical products that large numbers of Canadians use for prevention, such as hormone replacement therapy for women, or statins, need different evidence from those used in life-threatening conditions. Many witnesses also supported the

use of conditional or probationary licensing to allow more rapid entry of so-called “extraordinary need” pharmaceuticals that may be considered too risky for the general population but could provide benefit to the smaller populations with unusual disorders. In all cases, witnesses called for ongoing post-market collection of evidence accompanied by open dissemination through a neutral organization about the product risks and benefits.

B. Progressive Licensing in the Post-market Phase of the Life-cycle

Progressive licensing was presented as a critical element of proposed reform for post-market surveillance of pharmaceuticals. Officials from Health Canada’s Health Products and Food Branch told the Committee that progressive licensing would enable the regulator to constantly monitor a product once it was on the market. The underlying key premise was that, over time, there would be a progression in knowledge about every product. With this increase in knowledge would come the ability to more fully assess the benefits as well as the risks of pharmaceuticals.

Thus, Health Canada could impose requirements for the collection of knowledge about the pharmaceutical product over its entire life-cycle, starting in the pre-market phase with pre-established and progressive plans for well-designed clinical trials and post-market follow-up studies, for effectiveness monitoring, for safety surveillance and for identification and management of benefits and risks.

According to numerous witnesses, this life-cycle approach to the post-market reality of a pharmaceutical product would be an improvement over the current system, moving it from a relatively passive and reactive system to one that would more actively follow safety, efficacy and quality of products in the marketplace. Industry representatives indicated that progressive licensing would modernize Canada’s regulations to reflect emerging global standards and science. Many health professionals and consumers viewed progressive licensing as a means of getting innovative new pharmaceutical products onto the market as soon as possible while respecting the safety of users. Through ongoing assessment, the regulatory authority would be able to act quickly to demand changes by the manufacturer and the withdrawal of a product that was too risky for users in spite of the potential benefits.

Representatives of the pharmaceutical industry as well as other witnesses indicated that progressive licensing conforms to current international approaches. They felt that this harmonization of standards would allow greater access to international databases and increased consistency of post-market standards, especially for post-market clinical trials and other follow-up studies. In the United States, the Food and Drug Administration reported that it recently amended its legislation to require a single review 18 months after a product received market approval or after a product was used by 10,000 patients. Other witnesses pointed out that, in Europe, there is now a requirement for a reassessment of every product every five years.

However, other witnesses stressed that the life-cycle approach should not permit a loosening of pre-market approval criteria, indicating that it was acceptable only if preceded by a rigorous approval process. They wanted assurances that progressive licensing would not lead to more lenient conditions for pre-approval or licensing for pharmaceuticals. Some witnesses cautioned against using progressive licensing as an excuse to replace or reduce the randomized, double-blind trials that have traditionally been the gold standard for pre-market approval. Many witnesses emphasized that the real-world use of a product involves diverse populations where individual characteristics can result in unexpected outcomes and thus challenge the pre-market determination of benefits and harms. Overall, they urged ongoing work to build the systems that would include mechanisms for ongoing surveillance, transparency and accountability.

C. Distancing Post-market from Pre-market

At present, Health Canada's Health Products and Food Branch (HPFB) encompasses the programs essential to regulatory activities around pre-market and post-market assessments and compliance. The key directorates are the Therapeutic Products Directorate, the Marketed Health Products Directorate, and the HPFB Inspectorate. The Therapeutic Products Directorate approves pharmaceuticals in the pre-market phase and works closely with the Marketed Health Products Directorate and the Inspectorate in the post-market phase. The Marketed Health Products Directorate conducts post-approval safety surveillance and assessment of signals and safety trends through adverse reaction reporting and analysis, and provides risk communications concerning all regulated marketed health products, not just pharmaceuticals. The Inspectorate works with these directorates to monitor compliance with regulated pre-market and post-market activities and, when necessary, takes enforcement actions.

A number of witnesses talked about the need for an organizational separation between the pre-market assessments and the post-market safety investigations of pharmaceuticals. The concerns about current structures within Health Canada covered several aspects.

Some witnesses felt that because both pre-market and post-market programs lacked base funding and faced continual funding reallocations, they would be forced to compete for scarce resources, often leaving post-market activities with less. One witness noted that in terms of resource and staffing allocations, the Therapeutic Products Directorate gets three times the funding and almost four times the staff of the Marketed Health Products Directorate.

Others called for an independent agency removed from any potential conflict of interest relations that might have developed between regulator and industry during pre-market activities. In particular, several witnesses proposed an independent investigative

safety board to oversee post-market problems related to consumer safety, pointing to the example of the separation between aviation regulatory authorities and airplane crash investigation boards.

In attempting to address the concerns about the cross-over between pre- and post-market activities at Health Canada, departmental officials asserted that in 2002 the creation of the Marketed Health Products Directorate was a clear commitment to independent post-market surveillance. They argued that the scientists in the Marketed Health Products Directorate who coordinate post-market activities have provided independent scientific evaluation distinct from the scientists in the Therapeutic Products Directorate who approve products for market. They insisted that each directorate has a separate budget. At the same time, they reassured the Committee that there are channels for ensuring effective communication throughout the regulatory life-cycle of a product. The Inspectorate works with both directorates to conduct investigations to verify compliance and follow-up on safety advisories, warnings, and recalls.

The departmental officials also talked about the establishment of an Expert Advisory Committee on the Vigilance of Health Products as a valuable independent external body. They felt that this Committee with its diverse membership would increase the external expertise available to the Health Products and Food Branch as well as providing a mechanism for public involvement.

SECTION THREE: POST-MARKET SAFETY

Safety evaluation in the post-market phase continues to assess real or potential harm that a particular pharmaceutical product could cause to the recipient when used alone or in combination with another product.¹ As in the pre-market phase, the type, level and scope of adverse events, reactions and hazards are balanced against the benefits of a product. With respect to safety, the Committee heard substantial evidence about adverse reactions to pharmaceuticals.

A. Adverse Drug Reactions and Serious Adverse Drug Reactions

The Committee heard that there are various definitions that may be used in different ways. Health Canada indicated that it wants to hear about all suspected adverse drug reactions and noted that the common understanding of the term is: “Any undesirable effect of a health product. This can range from a minor effect such as a skin rash to a life-threatening one such as liver damage.” The more technical term found in the Food and Drug Regulations that governs mandatory reporting by manufacturers defines **serious**

1 Health Canada, Access to Therapeutic Products: The Regulatory Process in Canada, 2006, http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/access-therapeutic_acces-therapeutique_e.html.

adverse drug reaction as a “noxious and unintended response to a drug, that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization.”

While manufacturers asserted that they know what constitutes a serious reaction and how to report it, other witnesses called for greater clarity. Some witnesses pointed out that the definitions matter less than the intent and the goals and the outcomes of adverse reaction identification and reporting need to be communicated more successfully.

B. Current Adverse Reaction Reporting

In 2002, Health Canada created the Marketed Health Products Directorate with a specific mandate for post-market surveillance. Since then Health Canada reported a continual increase in domestic adverse reaction reports, with a 17% increase in domestic adverse reaction reports in 2007. Nonetheless, several witnesses indicated that less than 10% of adverse drug reactions are reported. One witness suggested that, for vaccines, the number was less than 5%.

Health Canada officials told the Committee that at present manufacturers have a regulatory obligation to report serious adverse reactions to the Canada Vigilance Program’s National Office while health professionals and patients are encouraged to report voluntarily to any of its seven regional vigilance centres. When manufacturers get reports from health professionals, consumers, or literature scans, they must report anything that they are aware of to Health Canada within specified timelines. Health Canada gets, per year, approximately 17,000 domestic reports and 350,000 foreign reports; of these 66% of come from manufacturers.

Representatives of the pharmaceutical industry described a typical process where the individual report is taken by a drug safety expert in the pharmaceutical company who follows up each individual case with the health professional or others involved in the initial report to ensure accuracy and completeness. In addition to the submission of individual case reports, manufacturers prepare periodic safety update reports for Health Canada.

Organizations representing health professionals pointed out that voluntary reporting by health providers directly to Health Canada currently constitutes a portion of adverse reaction reports. Data provided by an organization representing consumers indicated a significant increase in consumer reporting of adverse drug reactions: in 1998, an estimated 7.1% of reports were contributed directly by consumers, and by 2006 this had increased to 24.2%.

With the exception of manufacturers, many witnesses pointed to a variety of concerns about the current reporting program. Some witnesses felt strongly that a non-response to a drug should be included in the definition. A large number of witnesses called for clarity on the definition of an adverse reaction, on what should be reported, on who could and should report, and on how any report would be analyzed.

C. Data Quantity and Quality

Health Canada's current database for information on adverse drug reactions is called MedEffect. In 2005, the department created the MedEffect Web site as a single window for timely safety information about drug products. At present, Health Canada accumulates individual reports in order to identify trends. Once it has identified a potential signal, then it does a further investigation. MedEffect also promotes an online reporting form, a toll-free phone number and fax line and, in the future, aims for postage-free mail-ins. In addition, the Public Health Agency of Canada has a database for adverse events following immunization with vaccines. This Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) collects information from provincial and territorial health departments, health care professionals and the pharmaceutical industry. Information is shared between the two databases.

Despite these efforts, a significant number of witnesses emphasized the need for improved access to the MedEffect database as well as increased feedback on reports submitted. Witnesses complained that they have no knowledge of the analysis that follows the collection of reports. Representatives from both health professionals and consumer groups reported that there is limited awareness about Health Canada's adverse drug reaction reporting program and no directed effort to increase the public knowledge.

Many witnesses found the current MedEffect database to be cumbersome, requiring users to sift through numerous individual reports in order to identify significant information. They noted that currently the database can only be searched by looking at each individual drug reaction report, with no summary analysis available. Health professionals and consumers talked about the need for effective mechanisms to ensure informed feedback to those who send in reports. They referred to a black box where the report goes in but there is no indication of whether it was useful.

All groups talked about the need to increase quantity and quality of adverse drug reaction data. Health Canada noted the importance of both elements. In particular, the department noted that quality is affected by who reports and how they report, for example, a full case report provided by a physician would note the rash, the drug dosage involved, the temporal relationship, and the seriousness of the health outcome.

The pharmaceutical industry emphasized that, while spontaneous or voluntary reporting of adverse drug events is valuable for detecting potential post-market safety signals, high quality information is essential to sound scientific decisions. Manufacturers emphasized that in order to assess the associated risk and the relationship of causality between an adverse event and a drug, they require all relevant information. They also expressed concerns about possible duplication of reports leading to falsely high attributions of risk.

Health professionals observed that, because a number of active conditions may result in treatment with several medications, it may be difficult to detect whether negative symptoms are related to medication or disease. Some also argued that the reporting of known or familiar reactions would do little to improve scientific knowledge or to permit more appropriate treatment of patients. Instead, they pushed for a reporting program to specifically target new products. They insisted that increasing the quality and richness of adverse drug reaction reports is more important than increasing the volume of clinically insignificant reports.

Witnesses generally pushed for greater quantity of reports with analysis useful to new pharmaceutical products being used in a broader population than those exposed in the clinical trial stage. They called for the data gathered to be readily available online and presented in a manner that offers greater meaning than mere compilations of reported events. It could then be used for consumer education, guideline writing, biomarker research and other purposes.

D. Proposed Mandatory Reporting for Hospitals

Health Canada told the Committee that mandatory reporting by hospitals would be a first step in increasing the quantity and quality of adverse reaction reporting. This proposal is contained in Bill C-51 where a new section 20.7 outlines that “A health care institution that belongs to a prescribed class of health care institutions shall provide the Minister with information about the adverse reactions of individuals who receive medical treatment from them that are associated with the use of therapeutic products.”

Departmental representatives noted that, at some stage, people who suffer a serious adverse event will be hospitalized, making the information readily available for analysis. They indicated that consultations with provincial and territorial partners revealed that several provinces were already putting critical reporting systems into their hospitals or regional health authorities. On this point, one witness reported that Quebec in 2002 followed by Manitoba in 2005 passed legislation that required health care institutions to report all drug side effects as health care accidents. Departmental representatives also pointed out that they were examining systemic approaches using teams in hospitals, noting that the Canada Patient Safety Institute already encouraged development of such systems by involving groups and moving away from individual responsibility.

The Canadian Society of Hospital Pharmacists addressed the issue of hospital reporting directly, arguing that mandatory reporting in hospitals would create an avalanche of data but contribute little to overall knowledge about medications and adverse reactions. Representatives suggested that much of the new data would concern well known and anticipated adverse reactions; for example, serious bleeding experienced by patients on the blood thinner warfarin or low blood cell counts from patients undergoing chemotherapy. They used these examples of anticipated adverse reactions to explain one reason why less than 2% of adverse reactions leading to hospital admissions are reported to Health Canada. In addition to having valuable data lost or diluted by reporting excessive quantities of already known information, they worried about the potential strain and increased workload for health professionals who work in hospitals and related care settings.

One witness involved in research into the way genetics mediate drug reactions (pharmacogenomics/pharmacogenetics) talked about the merits of an active system of hospital reporting where dedicated, trained staff track, document and monitor adverse drug reactions. In this case, clinicians within children's hospitals across the country are paid to find cases of adverse drug reactions, to find matched patients who have not had drug reactions and to look at the genetic differences between them. This process involved getting people engaged and trained, not in regulating a mandatory system of reporting.

E. Spontaneous/Voluntary Reporting by Health Professionals

With reference to individual health professionals, Health Canada officials acknowledged that, internationally, evidence showed that mandatory reporting requirements have not led to increased quantity or quality of reporting. For support, they pointed to the 2005 survey of countries that regulate mandatory reporting for health professionals. They also expressed concerns about creating an additional burden for healthcare professionals who are already in short supply. The department also pointed out that there are jurisdictional issues as health professionals practice under provincial and territorial authority.

The vast majority of witnesses supported the general idea of having health professionals provide increased levels of adverse reaction reporting. The differences lay in whether the reporting should be voluntary or mandatory, whether all adverse reactions or only serious ones should be reported, whether the reporting process would be time-consuming or quick to execute, and whether the reporting system would actively assist reporting or penalize non-reporting.

The pharmaceutical industry emphasized that while spontaneous reporting of adverse drug events is valuable for detecting potential post-market safety signals, high quality information is essential to sound scientific decisions. They suggested improved training of health care professionals and the use of internationally accepted standard forms to increase detailed and accurate reporting.

Several witnesses expressed concerns about the ability to enforce mandatory reporting, questioning whether Health Canada had the jurisdictional authority and sufficient resources for compliance efforts. Another witness pointed out that many provinces already have various regulatory avenues — bylaws and standards of practice — whereby health professionals such as pharmacists are expected to report adverse drug reactions. For example, British Columbia has a bylaw requiring various actions including a report to Health Canada's B.C. regional reporting centre while Ontario has a standard of practice for compliance with any formal adverse reactions reporting programs.

Multiple witnesses referred to the 2005 Health Canada discussion paper *Designing a Mandatory System for Reporting Serious Adverse Reactions*. They noted the challenges identified with mandatory reporting by individual health professionals. These included lack of training in recognizing adverse reactions, lack of awareness about the existence and benefits of a reporting system, lack of time to report, and lack of familiarity with the reporting process.

In the absence of evidence from other jurisdictions that mandatory adverse reaction reporting by health professionals supports improved patient safety and before launching a program with no proven success, witnesses called for significant efforts to increase voluntary reporting. They pushed for the establishment and aggressive promotion of education and training programs for multi-disciplinary teams of pharmacists, physicians and nurses. They wanted Health Canada to invest in a real-time electronic adverse drug reaction system, a simple-to-use reporting system that would fit into the busy practices of health providers and that would integrate reporting forms into the software used by health care professionals at the point of care. They urged federal investments in research relating to the detection, evaluation and reporting of adverse drug reactions as well as support for decision-making on prescribing and utilization.

Groups representing consumers insisted that patients need to be part of the whole post-market system of communication and dissemination. They called for a system of voluntary reporting of adverse drug reactions that would work for them and wanted more efforts by Health Canada to increase their awareness of where and how to report. Even those who are currently attentive to the warnings and other information provided by Health Canada noted the absence of feedback when they do report. They consistently called for patient-and public-friendly information that facilitates understanding and enables involvement throughout the post-market stage.

SECTION FOUR: POST-MARKET EFFECTIVENESS

There are subtle differences between efficacy and effectiveness. Where efficacy in the pre-market phase determines the benefit a particular pharmaceutical product brings when it is taken in the context of a controlled environment such as a clinical trial,

effectiveness is determined by whether a product achieves the desired benefit for the intended population when prescribed, dispensed and taken under real life circumstances.² With respect to effectiveness, witnesses focused largely on utilization in the real world and the need for information.

A. Efficacy to Utilization Effectiveness

The Committee heard that active surveillance goes beyond reporting adverse reactions to studying the post-market effectiveness of pharmaceutical products. This means looking at whether or not they actually provide the expected benefit. At present, Health Canada assesses pre-market efficacy of a product on the basis of clinical trial evidence. The current post-market surveillance systems such as the MedEffect database are not focused on effectiveness after marketing.

Witnesses observed this gap between the efficacy demonstrated in clinical trials and the effectiveness in real world use. They generally agreed that, while a product may be efficacious in a controlled clinical trial setting, the true effectiveness of many commonly used pharmaceuticals may not be known when they are initially marketed to the general population. They emphasized that pharmaceutical products need to be tested on the populations that are actually going to be using them and that standards for effectiveness need to be based on the specific population receiving the product and the expected health goal for the product.

Health professionals noted that they do observe the effectiveness of the drugs that they prescribe or dispense and they were emphatic that an unwanted effect of a marketed drug must be part of the monitoring system. For them, a failure to achieve positive results and to provide the expected benefit is a serious negative outcome along with adverse outcomes that are known or those that are unknown and unexpected. They pointed out that as many as one third of drug treatments may be stopped early due to the ineffectiveness of the prescribed product.

B. Clinical Trials and Additional Studies

Health Canada noted that, as one of its initiatives important to post-market effectiveness, it had enhanced clinical trial oversight. This reference encompassed the newer regulatory requirements for clinical trials on drugs that were added since 2000. At present, before Health Canada licenses a new drug for a specific condition or disease, the pre-market approval phase calls for successful completion of three phases of clinical trials. In general, Phase 1 involves a small number of people and assesses drug safety; Phase 2 involves a larger group randomly divided into a treatment group and a control (usually

² Health Canada, Access to Therapeutic Products: The Regulatory Process in Canada, 2006, http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/access-therapeutic_acces-therapeutique_e.html.

placebo) group and assesses drug efficacy; Phase 3, with a very large group, is randomized, double-blinded, long-term and gives data on drug efficacy, benefits and adverse reactions. After successfully completing Phase 3 testing, the drug is ready to be reviewed for approval.

Health Canada also mentioned that it was seeking ways to call for post-market studies as a condition of licensing. The license would be issued based on the available science and manufacturers would be required to continue post-market surveillance, to reassess the product, and to submit follow-up studies. In addition, the department would assemble data from international regulatory bodies, utilization information from provinces and territories and involve academics in assembling a fuller picture. In Bill C-51, section 19.9 permits the establishment of regulations to require market authorization or establishment licence holders to compile additional health and safety information and report to the Minister.

Witnesses stressed that the information available from pre-market clinical trials often did not reflect the real world experience of use. They noted that clinical trials provide evidence that a pharmaceutical product can work but not always how well it will work in routine clinical practice. They stressed that there is currently a regulatory gap between the acquisition of pre-market data from randomized controlled trials for efficacy and the post-market data needed to determine if and how well a product works in the real world. They also stressed that notifications about all the studies (pre- and post-market) should be available to the public so that there was a record when studies started, ended or were abandoned.

Multiple witnesses called for obligatory post-market studies regulated by Health Canada to assess effectiveness as well as safety. Some suggested that another phase of clinical trials is needed after a drug is on the market in order to understand how to make the use of a drug safer or more effective. Health professionals in speciality areas recommended phase four, or post-approval, trials to confirm treatment results in the specific populations such as those with cancer and increased translational research to identify the subsets of patients that benefit from these new drugs.

Some witnesses wanted head-to-head trials with other drug products to get a clearer understanding of the overall effectiveness and safety profile compared to other products that may be used to treat similar conditions. They emphasized repeatedly that with clinical trial data, the patient groups are very limited while in actual practice, subgroups of patients are very diverse. The patients in the real world may be sicker, have other medications, and multiple co-illnesses along with the primary condition under treatment.

Overall, witnesses called for more large scale, real world effectiveness trials that were randomized but included some confounding issues and an active drug comparator, not just a placebo. They also saw a role for observational studies including patients with different histories, additional drug use, and other factors and using inexpensive

administrative data that includes utilization, co-therapies, adherence, etc. A few witnesses mentioned primary data collection using patient charts together with detailed clinical information that is also linked to administrative data.

When asked about who should pay for the post-market studies, several witnesses emphasized that it is important to distinguish between who should pay for the studies and who should conduct them. The primary goal would be to conduct studies that are valid and publicly accessible using the best possible expertise. It was argued that the research should be conducted by arms-length organizations while the research funds should come from the pharmaceutical companies as the entities that manufacture the products and that benefit financially from their use. Italy was mentioned as one example of a country where manufacturers contribute the equivalent of about 5% of their promotional budget to the Italian medicines agency to fund post-market research by university and clinical researchers. It was emphasized that there must be regulatory authority to compel the post-marketing studies as international evidence, particularly that from the United States, showed that manufacturers failed to produce the promised post-marketing studies about 50% of the time.

Health Canada assured the Committee that with the life-cycle approach it would monitor pharmaceutical products past the clinical trial phase and out into the real world where people using them may be very young, very old, and with a number of other health conditions. With respect to signals picked up through MedEffect, officials raised the possibility of doing post-market studies. They mentioned talking to foreign regulatory bodies and assessing utilization data to get a fuller picture.

C. Databases Assessing Effectiveness

Health Canada's MedEffect database collects information on the use of drugs primarily through reports on adverse drug reactions. The principal focus is on safety rather than effectiveness. In addition, Health Canada supports the Canadian Institute for Health Information (CIHI) in its development of two new databases in the pharmaceutical area. The National Prescription Drug Utilization Information System, (NPDUIS) involves collaboration with the Patented Medicine Prices Review Board (PMPRB) and the Canadian Medication Incident Reporting and Prevention System (CMIRPS) includes collaboration with Health Canada, the Canadian Patient Safety Institute (CPSI), and the Institute for Safe Medication Practices Canada (ISMP).

The National Prescription Drug Utilization Information System (NPDUIS) was funded in 2002 to provide critical analyses of utilization as well as price and cost trends. As of February 2008, NPDUIS included drug claims data from the provincial public drug plans in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Of the six drug plans at the federal level, only the Non-Insured Health Benefits Program of Health Canada was currently participating although their data is not yet in NPDUIS.

Overall, the NPDUIS database provides access to standardized information on prescription drug use and costs from across jurisdictions, incorporating drug product information from Health Canada's drug product database as well as formulary and plan information from public drug plans. This information has many uses including analysis of the impact of policy decisions on utilization; analysis of trends in utilization over time and across jurisdictions; and other new knowledge. An additional component with claims data includes information such as what drug was dispensed, when, to which person, where, who prescribed the drug, how often the prescription was filled, how much of the drug was dispensed, and how much it cost.

CIHI provided an example of how the NPDUIS data was used to identify trends in potentially inappropriate medication use among seniors. The analysis examined claiming patterns for seniors on public drug programs in Alberta, Saskatchewan, Manitoba, and New Brunswick. Specifically, it calculated the proportion of seniors on public drug programs who were using drugs that were internationally recognized as potentially inappropriate for seniors due to the elevated risk of adverse events such as those on a list developed by gerontologist Dr. Mark Beers.

CMIRPS is expected to be ready for pilot projects in September 2008. As currently designed, it will not capture adverse drug reactions but will capture medication incidents, system errors caused by inappropriate human actions, such as the patient being given an incorrect medication or the wrong dose of a medication in a hospital setting. Data collected by trained teams in hospitals will be submitted to CMIRPS for analysis to inform systems and process redesign, which in turn will make it possible to deliver safer patient care.

Witnesses noted that there is a lot of information in Canada about drug use and multiple bodies across the country and around the world collecting such data. What they did not see was a national body that could pull all the information together, analyze it, synthesize it into policy, and disseminate it to health providers and the public. They stressed the need for a more coordinated and standardized approach to data collection on effectiveness at the post-market phase. It is difficult to know what the publicly accessible register included in Bill C-51 will encompass. The bill, under subsection 20.8, allows the Minister to establish and maintain a publicly accessible register with prescribed information about therapeutic products.

D. Drug Effectiveness and Safety Network

Health Canada pointed out that it is working with provincial and territorial colleagues, as well as networks of academic centres, to develop a real world drug effectiveness and safety network. This initiative is part of the National Pharmaceuticals Strategy and direction from First Ministers in the 2004 10-year plan to strengthen healthcare. A 2007 consultant's report, *Medicines that Work for Canadians: Business Plan*

for a *Drug Effectiveness and Safety Network*,³ provided a model for a national oversight body of key stakeholders in all jurisdictions and the development of a national network of centres of pharmaceutical research excellence.

The proposed business plan recommended that the program initially be funded for a five-year period, at a cost of approximately \$20 million annually, to be run through the Canadian Institutes of Health Research. It further recommended that the program build a national co-ordinated network for post-market surveillance and research into the real world safety and effectiveness of medicines, maximize the benefits afforded by the data resources available in Canada, and develop research capacity to permit prompt response to real needs for information in a timely fashion.

According to witnesses, this model would provide another source of data for the regulator to understand real world impacts of pharmaceuticals, both on effectiveness and on safety. Centres of excellence in pharmacoepidemiology, for example, could carry out priority research with those diseases that affect a large population and that require long-term medication, such as heart disease and depression.

Supporters of the business plan concept saw advantages in the ability to fund more clinical trials, the various research tools that could be used to evaluate and monitor drug safety and effectiveness, the way that centres across the country could link with practitioners, the improvements for communication and provision of information, and particularly the ability to access independent information about the benefits and risks of drugs.

SECTION FIVE: POST-MARKET QUALITY

In general, quality with respect to post-market surveillance applies to aspects related to product content and stability, labelling clarity and consistency, and other standards applied in product manufacturing, testing, and storage.⁴

3 Gary Fox and Nicolaas Otten, Donna Cona Inc., for Health Canada, February 2007. The project was a collaboration between the National Pharmaceuticals Strategy, the Canadian Institutes of Health Research and the Canadian Drug Policy Development Coalition. For more information, see: http://www.hc-sc.gc.ca/hcs-sss/pubs/pharma/2007-med-work_eff/index_e.html.

4 Health Canada, *Access to Therapeutic Products: The Regulatory Process in Canada*, 2006, http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/access-therapeutic_acces-therapeutique_e.html.

A. Packaging, Labelling and Other Quality Issues

The primary evidence about quality issues was derived from reports by the CIHI and the Institute for Safe Medication Practice. Both organizations referred to the data collected anonymously and voluntarily in CMIRPS with funding by Health Canada. Both organizations also talked about efforts to understand and prevent medication incidents that may be linked to naming, packaging, labelling, look-alikes, and sound-alikes in marketed drug products.

The Institute for Safe Medication Practice works collaboratively with various health organizations to promote safe medication practices and provided some specific examples of quality-related problems and actions. These included:

- a) a transdermal patch that was almost invisible, leaving practitioners in emergency departments unaware that patients were receiving a highly potent narcotic; the manufacturer responded by adding both the name and colour to the patch;
- b) two bags filled with liquid, one intended for pharmacy use only and one intended for intravenous use, were mixed during use, leading to serious harm; the manufacturer changed their labels;
- c) two similar ampoules were inadvertently switched; the manufacturers improved the labelling;
- d) a label meeting regulatory requirements for display of concentration provided product information in millimoles while physicians prescribe in grams; finding the conversion calculation to be difficult, the manufacturer changed the label, removing its logo to give prominence to critical information;
- e) five neuromuscular blocking agents identified as high-alert drugs with the potential for harm if error; three manufacturers voluntarily placed a warning on the vial and two did not.

B. Warnings, Advisories and Recalls

The Inspectorate is a key player in the assessment of post-market quality through its surveillance, inspection and investigation activities. It has authority through product licensing as well as licensing of manufacturing facilities to enforce compliance on good manufacturing practices and standards related to the product's content, labelling and other issues. Investigations and other actions can be initiated following signals picked up through MedEffect or through external complaints and reports.

Both organizations indicated that Health Canada in its regulatory role had a major interest in the incidents or errors that are associated with post-market use of approved products. They distinguished between the type of product-related errors outlined above and system-related errors such as patient identification incidents. They supported voluntary actions by manufacturers but saw the need for regulatory changes, including standards and guidelines that would ensure the incorporation of labelling, packaging, and other issues in future manufacturing practices. In addition, both emphasized the need to collect data that would permit analysis of factors related to product related errors.

Health Canada representatives did not talk about how CMIRPS information would be used to regulate these product-related concerns. They did note that the MedEffect Web site provided access to the latest advisories, warnings and recalls, issued by Health Canada concerning therapeutic drugs. They also told the Committee that at present, Health Canada does not have the authority to recall drugs for safety, effectiveness or quality concerns.

At present, while the regulator could withdraw the manufacturer's licence to sell the product, it generally works with the manufacturer to get voluntary compliance to adjust a product or to take a product off the shelves. Bill C-51 proposes a new requirement through section 20.1 aimed at label revisions and new sections 23.9 and 24 could allow an inspector to authorize removal or recall of a product if it does not meet requirements under the Act or presents a serious or imminent risk of injury to health.

SECTION SIX: ADDITIONAL POST-MARKET COMPONENTS

A. Direct-To-Consumer Advertising

At present, direct-to-consumer advertising of prescription drugs is substantially prohibited. A 1978 amendment to the prohibition permitted name, price and quantity information of prescription drugs to be provided to the general public. Two types of prescription drug messages are currently allowed: reminder ads and help seeking messages.

Some witnesses voiced their support for the existing prohibition, and none suggested any changes to lessen the restrictions. Bill C-51 provides an indication that there is no intention of changing the prohibition since section 15.1(2) moves the prohibition from regulation into legislation. Those witnesses who expressed frustration over what they perceived to be a lack of enforcement of the existing prohibition may welcome the increased fines, penalties and terms of imprisonment proposed in Bill C-51 as a deterrent to those who consider ignoring the prohibition.

B. Privacy and Confidentiality

The discussion of post-market surveillance brought continuous references about the need for shared electronic records and databases and with this came concerns about privacy and confidentiality. Adverse drug reaction reporting and related databases, electronic prescribing, electronic health records, pharmacists databases, federal and provincial drug plans, clinical trial registries, etc. — all these raised issues about access to information and privacy.

While Health Canada currently maintains a national adverse drug reaction database, drug companies and individual consumer groups manage patient registries with similar information. Drug utilization data is collected by organizations ranging from the Canadian Institute for Health Information with the NPDUIS data to a consulting group claiming to have the largest database in the country related to prescription drug use. Canada Health Infoway is planning to have an electronic health record available for 50% of Canadians by 2010.

Most organizations involved in data collection maintained that they can do this without jeopardizing privacy. They talked about safe and secure storage of data, agreements on which data can be shared or disclosed, non-identification of the patient, and for governments, an obligation to perform a privacy impact assessment with each new program.

Nonetheless, the Committee also heard that “re-identification” has become an issue in recent years. This refers to the ability of combining information from different sources in order to establish identification. Re-identification has become possible due to increased digitization of health data and surveillance programs and the proliferation of publicly accessible information on the Internet and sophisticated technological capacity to link up information across different databases.

It is unclear whether Bill C-51 will address any of these privacy concerns. The main reference in subsection 20.9 would permit the Minister to disclose personal information to a person or government without the individual’s consent.

C. Off-label Use of Pharmaceuticals

Health Canada indicated that the approval process involves submission of evidence of efficacy in particular clinical situations and the approval is subsequently specific to the indicated use. New indications for use of a drug may be added to a drug's label and accompanying information about indications for use but this must be done through a supplementary new drug application with supporting evidence. Currently the department does not have authority to control so-called "off-label" uses for marketed products. Off-label use occurs when a drug licensed for a particular use or indication is found to be effective when used for other medical conditions.

If the manufacturer has not submitted the appropriate clinical trial evidence to support the new uses, the drug is prescribed by physicians for medical uses that were not part of the original Health Canada approval. Witnesses indicated that off-label use is generally a decision taken by a physician, usually on the basis of available scientific evidence but with the absence of specific clinical trials by the responsible pharmaceutical company. Some noted that such uses allow for innovations in practice and provide different treatment options. Others argued that off label uses compromise evidence-based health practices, affect regulatory safety and efficacy expectations and undermine incentives for manufacturers to conduct rigorous studies.

The Committee heard that while off-label drug use is not in itself illegal, Health Canada has authority to limit marketing by pharmaceutical companies of products for specific uses that have not been approved and also has labelling authority to include cautionary alerts about use. It is unclear whether Bill C-51 might provide room to address some of this issue.

D. Consumer Participation

Representatives of consumer and patient groups wanted opportunities to offer their perspectives and experiences in the decision-making process around post-market surveillance. They talked about the need for more and better information about the safety and effectiveness of pharmaceutical products. They wanted more consultation and direct involvement in regulatory endeavours.

Witnesses cited the establishment of Health Canada's Office of Consumer and Public Involvement in 2005 as an example of the Department's increased commitment to greater transparency and increased consumer involvement in decision-making about product safety. In this regard, several witnesses acknowledged their participation in consultations on the progressive licensing framework and their work on drug safety committees.

Others wanted a process put in place for genuine citizen engagement at all stages of the life-cycle of a pharmaceutical product. They called for dedicated resources and funding aimed at consumers to ensure their participation at the clinical trial stage as well as after licensing of products. They envisioned education, increased awareness and training as essential to appropriate reporting of adverse reactions. One witness observed that women could be a target of adverse reaction awareness efforts as women are more likely to report than men, doing so both on their own behalf and on behalf of family members.

The Committee also heard that funding could be directed to community-based education efforts, to media promotion and to the establishment of a national clearing house for information — all independent of the pharmaceutical industry. The focus was to be on government-approved, unbiased information geared toward different literacy skills. One witness suggested using community health centres as a venue for such efforts.

E. Vaccines

Before the creation of the Public Health Agency of Canada, vaccines and drugs were both dealt with by Health Canada. At present, the Public Health Agency of Canada has primary responsibility for post-market surveillance of preventative human vaccines. However, it interacts frequently with Health Canada's Biologics and Genetic Therapies Directorate that does pre-market approval of vaccines as well as some post-market risk assessments. It was also noted that while the Public Health Agency of Canada does have a database to collect information on adverse events of vaccines, the ultimate responsibility for informing manufacturers rests with Health Canada's Marketed Health Products Directorate. Thus, the warnings about adverse reactions are usually sent by Health Canada.

Although the Department and the Agency asserted that they work very closely together on vaccines, the separation between the respective roles of Health Canada and the Public Health Agency raised concerns about their communication abilities. In the particular case of Gardasil, the vaccine recently marketed for prevention of cervical cancer, it was suggested that Health Canada was unaware of the monitoring activities by the Public Health Agency that followed reports of two deaths by the European Agency for the Evaluation of Medicinal Products. The possibility of the two entities working in isolation and the lack of research about the long-term effects for young women and men associated with this new product led to calls for systemic data collection on all recipients of the vaccine.

SECTION SEVEN: COMMITTEE OBSERVATIONS AND CONCLUSIONS

A. Adverse Drug Reaction Reporting

The Committee heard clearly that adverse drug reaction reporting, whether mandatory or voluntary, needs to produce data of high quantity and quality. It also heard that this can be achieved through measures other than by imposing mandatory reporting. Health professionals and consumers indicated that they would respond to a number of motivational incentives.

1. Key Elements for Effective Adverse Reaction Reporting

In the Committee's view, the key elements that need to be reinforced to encourage and promote voluntary adverse reaction reporting by health professionals as well as the public include:

- a) **Teams:** The need to mobilize teams of health professionals is crucial. These teams could include physicians, pharmacists, nurses and other individuals who are trained to identify, assess, report and analyze adverse reactions. This would require fostering interprofessional collaboration with clearly identified roles. Hospitals could build on the experience of those that currently have reporting mechanisms through voluntary medication incident reporting, through quality control or research-directed teams.
- b) **Training:** Health professionals and consumers expressed a need both for basic information about reporting processes and for more interactive instruction that would instill useful skills that individuals could then customize to share with others. They favoured hands-on training through health service and community organizations as well as professional regulatory bodies.
- c) **Feedback:** Individuals, both consumers and health professionals who submit adverse drug reaction reports, deserve timely feedback as well as appropriate communication about the ongoing analysis of data. Currently, reports are sent to what is described as a "black hole." This negative assessment can be overcome by creating a communication loop that rewards input from organizations and individuals with an acknowledgement that

the report was received. In addition to direct feedback, other communication can take place through local and national media, departmental Web sites, sessions at medical schools and continuing medical education, and targeted public awareness campaigns providing information regarding the analyses of the reports.

- d) **Standardization:** Standards for definitions, reporting criteria, reporting forms within Canada and internationally, timely processing of reports, attentiveness to new drugs, warnings and advisories, and for timeframes around adverse drug reactions are needed. For example, the issue of reporting on newly marketed products raised the notion of using a symbol such as the black triangle used in the United Kingdom to send a recognized signal to physicians to be more responsive to reporting side effects. A similar approach could provide the Canadian public with a signal that a product is new to the market and that greater vigilance in adverse reaction reporting could be beneficial.

- e) **Phased-in Approach:** Given that the establishment of the CMIRPS reporting system has taken several years to reach pilot phase, effective adverse reaction reporting and the goals for quantity and quality will likely also take several years to achieve. While Health Canada reported ongoing consultations with provincial and territorial governments, hospitals, health professionals, and the general public need time to understand the value of reporting.

- f) **Ongoing Support:** Reporting of adverse reactions takes time from busy work and other schedules. A move to electronic reporting requires technology that is not only expensive to acquire and maintain but also requires training to use. Individuals who do report adverse reactions may experience system problems and will want to communicate directly with someone on the receiving end. All of these things suggest that a commitment of ongoing support is required from the federal regulator.

- g) **Citizen Engagement:** Informed involvement by all participants could contribute to the development of an adverse reaction reporting system. While the pharmaceutical industry currently has mandatory reporting obligations, health professionals and members of the broader public could be actively engaged by Health Canada in exploring

ways to achieve better voluntary reporting outcomes. At present, activities to develop a targeted surveillance system to stimulate reporting by pediatricians and a chronic disease reporting system with patient groups operate in this vein.

2. Hospitals and Adverse Drug Reaction Reporting

The Committee is unclear about Health Canada's proposal for mandatory reporting of adverse drug reactions by hospitals. Health Canada referred to the jurisdictional problems of mandatory reporting without any indication of how these would be overcome. It pointed to the actions by some provinces to collect incident data without specifying whether these have been assessed for effectiveness. While it mentioned systemic team approaches developed with respect to patient safety, it did not provide particular examples.

The Committee is aware that Quebec and Manitoba may already have evidence that could be analyzed to determine the effectiveness of mandatory reporting of incidents in hospitals. It believes that Health Canada can enhance hospital adverse reaction reporting while taking into account the structured legal framework in these two provinces to avoid any duplication of efforts or jurisdictional intrusion. The Committee also acknowledges the ongoing work to build and sustain a reporting network related to children and pharmacogenetics as well as the upcoming pilot on medication incident reporting through CMIRPS. These ongoing demonstrations of elements that work could be analyzed and used along with other pilot examples to determine best practices in order to make reporting effective in hospitals.

The Committee also acknowledges the direct federal responsibility in this area. As the Auditor General of Canada pointed out in the 2004 report on federal government drug benefit programs, the federal government is the fourth largest payer of prescription drug benefits in Canada, after Ontario, Quebec, and British Columbia. At that time, it was estimated that the federal government spent more than \$430 million annually on prescription drugs for about one million Canadians. These Canadians included clients served by six federal organizations: Health Canada (benefits for First Nations and Inuit), Veterans Affairs Canada (veterans), National Defence (Canadian Forces members), the Royal Canadian Mounted Police (members), Citizenship and Immigration Canada (certain designated classes of migrants), and Correctional Service Canada (inmates of federal penitentiaries and some former inmates on parole).

3. Conclusions

In light of these concerns, the Committee recommends that:

RECOMMENDATION 1

The Government of Canada/Minister of Health enhance voluntary reporting of adverse drug reactions by incorporating the key elements listed above as well as providing accessible information such as the Health Canada 1-800 number and Web address to all areas of interaction between health professionals and consumers.

RECOMMENDATION 2

The Government of Canada/Minister of Health in conjunction with provincial and territorial counterparts support educational training programs for health professionals aimed at increasing adverse drug reaction reporting, while respecting provincial jurisdiction.

RECOMMENDATION 3

The Government of Canada/Minister of Health establish a specific transition fund to provide money to existing initiatives and to establish other pilot projects across the country to build evidence on effective adverse drug reaction reporting in hospitals.

RECOMMENDATION 4

The Government of Canada through the Federal Healthcare Partnership examine ways to enhance reporting of adverse drug reactions in all health institutions that serve federal health client groups (i.e. Department of National Defence health centres on bases, Health Canada health centres on First Nations reserves, Veterans Affairs Canada contract hospitals and Correctional Services Canada facilities).

RECOMMENDATION 5

The Minister of Health immediately initiate work on adverse drug reaction reporting within Health Canada's First Nations on-reserve health centres and nursing stations.

RECOMMENDATION 6

The Government of Canada/Health Canada ensure that all pilot projects to build adverse drug reaction reporting incorporate funding for technological tools required to increase reporting by health professionals (physicians, pharmacists, nurses, etc.) in their daily practices.

RECOMMENDATION 7

Health Canada take measures to efficiently analyze the adverse drug reaction data collected through the MedEffect Web site and make the analyses available in a form that is accessible to health professionals and the public.

RECOMMENDATION 8

The Government of Canada/Health Canada enforce the existing mandatory requirement for the pharmaceutical industry to report serious adverse drug reactions both within Canada and internationally, increase efforts to acquire reports on suspected adverse drug reactions and make all the information available publicly.

B. Effectiveness and Safety Research

The Committee heard that there were ongoing consultations to establish a network of research centres across the country to look at the use of drugs in the real world and to understand their safety and effectiveness after marketing. In addition to the establishment of a national oversight body composed of key stakeholders, the plan would also set up a national network of centres of pharmaceutical research excellence.

1. Key Elements for a Research Network

In the Committee's view, the establishment of a research network examining post-market effectiveness and safety must consider the following key elements:

- a) **Multi-populations:** Some researchers already focus on post-market surveillance of safety and/or effectiveness through studies looking at a wide range of populations. Thus, some research work looks at general utilization and effectiveness or safety in the general population or in special populations such as seniors, women, or children. For example, Health Canada is currently working with the

Canadian Paediatric Society to develop a Canadian pediatric surveillance program to collect information from 2,300 pediatricians and sub-specialists on a monthly basis. Other work examines the effect of drugs in certain disease groups such as those with cancer, anemia, arthritis, HIV/AIDS, etc.

- b) **Multi-disciplines:** In addition to post-market clinical trials and head-to-head trials with other products, studies involving observation, primary data collection, and administrative data analysis were mentioned. As well, subject areas of specialization such as pharmacogenetics and pharmaco-epidemiology and sex/gender analysis were all seen as essential to collecting, analyzing and synthesizing information to guide health policy and regulation in this area.

- c) **Multi-sectoral Partnerships:** Universities and not-for-profit organizations, when partnered with industry and government, provide the kind of nation-wide and multi-sectoral arrangements that can work for Canadians. Canadian academic research, grassroots evidence, entrepreneurial talent and government support could be combined to further enhance the understanding of drug effectiveness and safety in the real world.

- d) **Funding:** The business plan for a drug effectiveness and safety network proposes that the cost would be about \$20 million annually to be operated under the Canadian Institutes of Health Research. The plan suggests manufacturers who stand to profit from the use of safe and effective drugs should contribute financially but should not be permitted to have control or influence over the findings.

- e) **Information Dissemination:** The centres could give a voice to the concerns and priorities of Canadians while also interpreting and communicating new knowledge about drug safety and effectiveness back to the public. To disseminate research findings creatively and appropriately, the process must involve the health care providers, academics, researchers, community organizations and policy makers.

2. Conclusions

With these concerns in mind, the Committee recommends that:

RECOMMENDATION 9

The Government of Canada/Minister of Health immediately establish the drug effectiveness and safety network, a national network of pharmaceutical research centres to operate under the Canadian Institutes of Health Research as outlined in the 2007 business plan.

RECOMMENDATION 10

The Government of Canada through the Canadian Institutes of Health Research encourage the network's research to be multi-disciplinary, to reflect innovative research such as pharmacogenetics and pharmacoepidemiology and to incorporate sex/gender analysis.

RECOMMENDATION 11

The Government of Canada, as the fourth largest pharmaceutical provider in Canada, examine the possibility, through the Federal Healthcare Partnership, of a centre of excellence for drug effectiveness and safety assessments for the six federal health client groups.

C. Electronic Databases

Over the course of the study, the Committee heard about many electronic databases with relevance to post-market surveillance and utilization of pharmaceuticals. These information collections that could be retrieved via a computer system included MedEffect at Health Canada, the Canadian Adverse Events Following Immunization Surveillance System at the Public Health Agency of Canada, the National Prescription Drug Utilization Information System and the Canadian Medication Incident Reporting and Prevention System at the Canadian Institute for Health Information. Each specialized system was identified as a tool that could provide significant information in the area of post-market surveillance generally and the understanding of drug safety and effectiveness particularly.

The application of these databases to post-market pharmaceutical surveillance is complemented by efforts through Canada Health Infoway to foster and accelerate the development and adoption of compatible electronic health information systems across the country. In particular, the work by Canada Health Infoway to support the development of electronic health records for individual patients was viewed as beneficial to ongoing

surveillance of drugs used in the real world by real patients. Thus, electronic prescribing could include patient diagnoses on the e-prescription. This, in turn, would enhance epidemiological data collection and analysis and, further, would offer insight into off-label uses of pharmaceuticals.

1. Key Elements for Effective Electronic Databases

In the Committee's view, all electronic databases in the context of post-market pharmaceutical surveillance must apply the following key elements:

- a) **Standards:** Efforts to improve post-market pharmaceutical surveillance require health information that is reliable and that can be generalized across data sets. The development and maintenance of standards with respect to definitions, organization of data, methods for integrating data, and other facets have crucial benefits. Standardization can reduce costs in design, support replication, and ensure efficient exchanges of data while protecting privacy.
- b) **Accessibility:** If post-market surveillance and utilization databases are to be useful, they must be accessible and ensure the ability to search, retrieve and analyze the information that they contain. Health professionals and consumers are willing to contribute to databases if they feel that they are getting something in return that will help them with decision-making. This accessibility also relates to real-time interchanges where access means that an encounter or consultation can involve some interaction between several parties simultaneously.
- c) **Linkable:** The need to have electronic tools that are capable of talking to each other with database linkages across the country (especially with federal and provincial governments) is critical. Linkages between databases allow individual jurisdictions to deliver local and regional solutions cost-effectively while contributing to a larger, interoperable national system. Linkages for health professionals could involve electronic prescribing that can then be used to understand pharmaceutical utilization, safety and effectiveness. For individuals and consumer health organizations, computer networks could permit greater sharing of information about drugs.

- d) **Privacy:** Canadians generally support the use of electronic databases but they also expect their privacy to be protected in the collection, storage and use of their personal health information. They want to know that any personally sensitive or identifying information is well managed and that they have some control over when and how the information is shared for secondary purposes. Continuous and ongoing efforts are needed to engage them in supporting electronic database uses for improvement in post-market surveillance while providing assurances of privacy.

2. Conclusions

In light of the issues outlined above, the Committee recommends that:

RECOMMENDATION 12

The Minister of Health establish a separate analysis and dissemination unit to analyze and to report regularly on post-market pharmaceutical surveillance data including findings, implications, subsequent actions, etc.

RECOMMENDATION 13

The Government of Canada build the electronic database capacity among its six federal formularies and facilitate linkages for analysis with respect to post-market drug safety and effectiveness.

RECOMMENDATION 14

The Government of Canada fund the ongoing engagement of professionals and the public in the study of privacy issues relevant to post-market surveillance.

RECOMMENDATION 15

The Government of Canada increase investments in Canada Health Infoway in order to accelerate the development of electronic health records and e-prescribing with the inclusion of diagnostic information.

D. Regulatory Resources

The Committee heard that expertise, skills and resources dedicated to post-market surveillance need to be readily available to detect safety problems with pharmaceuticals, to assess their effectiveness in the real world, and to ensure their quality on the market. Witnesses suggested that limited human, financial and infrastructure resources for post-market surveillance by Health Canada were at least partly responsible for inadequacies in the current system.

In 2002, Health Canada created the Marketed Health Products Directorate within the Health Products and Food Branch to provide consistent and post-market monitoring of some health products, namely drugs and vaccines as well as natural health products. In addition, Health Canada has a single Inspectorate of approximately 100 inspectors that must ensure both pre- and post-market compliance on all health products (NHP, cosmetics, medical devices, as well as drugs). Witnesses suggested that more resources are needed in order to efficiently collect and analyze data, to disseminate the findings to the general public, to strengthen post-market compliance and enforcement efforts, and to ensure an open and transparent system.

1. Key Elements for Post-Market Regulatory Resources

In the Committee's view, Health Canada must apply the following key elements when allocating post-market resources:

- a) **Separate and independent pre- and post-market activities:** At present, there does not appear to be a distinct separation between pre- and post-market pharmaceutical activities and resources at Health Canada in terms of funding and processes. On funding, the Auditor General of Canada reported that Health Canada's regulatory programs are generally underfunded and that funds designated for one activity are often transferred to another one. As well, the Auditor General indicated that an emphasis on enhancing and speeding up the pre-market approval of pharmaceutical products has resulted in greater allocation of funds to pre- as opposed to post-market activities. In terms of processes, because the Therapeutic Products Directorate conducts both pre- and post-market activities, there is a concern about a pre-market influence on post-market surveillance activities. However, it is important that the post-market lifecycle receive proportionate resources without jeopardizing the necessary care needed for pre-market assessments.

- b) **Strong Overall Compliance and Enforcement:** The fact that the current Inspectorate has multiple duties for pre- and post-market activities for pharmaceuticals as well as other products is a concern. The need for inspections that are specific to post-market regulated activities and thus capable of being carried out more frequently is important.
- c) **Engaged Stakeholders:** Resources are needed to enable other players in the system, including patients, professionals, and hospitals to serve a more meaningful role in post-market pharmaceutical surveillance. As well as active engagement exercises, there is a role for a national clearing house for information on post-market safety and effectiveness.
- d) **Increased Human and Physical Infrastructure:** The current infrastructure for post-market pharmaceutical surveillance activities includes personnel and equipment necessary for information gathering and processing, detection of signals related to potential adverse events, links with international bodies, and for work with additional partners. Health Canada has been building its capacity to process and analyze adverse drug reactions and to do other post-market activities through the Marketed Health Products Directorate since 2002 and MedEffect since 2005. It has also been working to increase its interactions with national and international counterparts on issues such as pharmaceutical counterfeiting. While slowly increasing capacity, more analysts and technical support are needed to truly make post-market surveillance an active rather than a passive exercise.

2. Conclusions

With respect to concerns about resources, the Committee recommends that:

RECOMMENDATION 16

The Government of Canada/Minister of Health allocate additional new funding for post-market pharmaceutical activities sufficient to:

- **build adverse drug reaction reporting requirements including but not limited to database development and maintenance, training, and communication strategies,**

- **establish monitoring and research for pharmaceutical effectiveness and safety,**
- **follow-up on advertising restrictions for pharmaceuticals,**
- **increase scrutiny of counterfeit pharmaceuticals including but not limited to investigations of adverse drug reactions, enforcement efforts, etc.**

RECOMMENDATION 17

The Government of Canada/Minister of Health allocate additional new funding specifically to increase post-market inspection and enforcement capacity for pharmaceuticals.

RECOMMENDATION 18

Health Canada explore the possibility of further distancing the human and financial resources required for pre-market activities for pharmaceuticals from those required for post-market activities.

LIST OF RECOMMENDATIONS

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The Government of Canada/Minister of Health enhance voluntary reporting of adverse drug reactions by incorporating the key elements listed above as well as providing accessible information such as the Health Canada 1-800 number and Web address to all areas of interaction between health professionals and consumers.

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The Government of Canada, as the fourth largest pharmaceutical provider in Canada, examine the possibility, through the Federal Healthcare Partnership, of a centre of excellence for drug effectiveness and safety assessments for the six federal health client groups.

RECOMMENDATION 12

The Minister of Health establish a separate analysis and dissemination unit to analyze and to report regularly on post-market pharmaceutical surveillance data including findings, implications, subsequent actions, etc.

RECOMMENDATION 13

The Government of Canada build the electronic database capacity among its six federal formularies and facilitate linkages for analysis with respect to post-market drug safety and effectiveness.

RECOMMENDATION 14

The Government of Canada fund the ongoing engagement of professionals and the public in the study of privacy issues relevant to post-market surveillance.

RECOMMENDATION 15

The Government of Canada increase investments in Canada Health Infoway in order to accelerate the development of electronic health records and e-prescribing with the inclusion of diagnostic information.

RECOMMENDATION 16

The Government of Canada/Minister of Health allocate additional new funding for post-market pharmaceutical activities sufficient to:

- build adverse drug reaction reporting requirements including but not limited to database development and maintenance, training, and communication strategies,**

- **establish monitoring and research for pharmaceutical effectiveness and safety,**
- **follow-up on advertising restrictions for pharmaceuticals,**
- **increase scrutiny of counterfeit pharmaceuticals including but not limited to investigations of adverse drug reactions, enforcement efforts, etc.**

RECOMMENDATION 17

The Government of Canada/Minister of Health allocate additional new funding specifically to increase post-market inspection and enforcement capacity for pharmaceuticals.

RECOMMENDATION 18

Health Canada explore the possibility of further distancing the human and financial resources required for pre-market activities for pharmaceuticals from those required for post-market activities.

APPENDIX A LIST OF WITNESSES

Organizations and Individuals	Date	Meeting
<p>Department of Health</p> <p>Meena Ballantyne, Assistant Deputy Minister, Health Products and Food Branch</p> <p>Diana Dowthwaite, Director General, Health Products and Food Branch Inspectorate</p> <p>David K. Lee, Director, Office of Patented Medicines and Liaison, Therapeutic Products Directorate</p> <p>Chris Turner, Director General, Marketed Health Products Directorate</p> <p>Michael Vandergrift, Director General, Policy, Planning and International Affairs Directorate</p>	2008/01/31	9
<p>BIOTECanada</p> <p>Philip Schwab, Vice-President of Industry Relations</p> <p>Canada's Research-Based Pharmaceutical Companies (Rx & D)</p> <p>Pier-Giorgio Fontana, Consultant, Regulatory Affairs</p> <p>Canadian Generic Pharmaceutical Association</p> <p>Jacqueline Conant, Principal Consultant, Pharmacovigilance, Apotex Inc.</p> <p>Colin D'Cunha, Director, Pharmacovigilance, Apotex Inc.</p> <p>NDMAC</p> <p>David Skinner, President</p> <p>Robert White, Director, Scientific and Regulatory Affairs</p>	2008/02/05	10
<p>Canadian Institute for Health Information</p> <p>Michael Hunt, Manager, Pharmaceuticals</p> <p>Glenda Yeates, President and Chief Executive Officer</p> <p>Patented Medicine Prices Review Board</p> <p>Brien G. Benoit, Chairperson</p> <p>Barbara Ouellet, Executive Director</p>	2008/02/07	11

Organizations and Individuals	Date	Meeting
<p>Canadian Pharmacists Association Jeff Poston, Executive Director Denis Villeneuve, Member of the Board</p>	2008/02/14	13
<p>Canadian Society of Hospital Pharmacists Myrella Roy, Executive Director</p>		
<p>National Association of Pharmacy Regulatory Authorities Karen Wolfe, Executive Director</p>		
<p>Ordre des pharmaciens du Québec Claude Gagnon, President Manon Lambert, Director General and Secretary</p>		
<p>Canadian Medical Association John Haggie, Chair, Board Working Group on Pharmaceutical Issues Samuel Shortt, Director, Knowledge Transfer and Practice Policy</p>	2008/02/28	14
<p>Canadian Men in Nursing Group Irfan Aslam, Vice President and Director of Finance James D'Astolfo, President and Founder</p>		
<p>Federation of Medical Regulatory Authorities of Canada Douglas Anderson, President Elect Fleur-Ange Lefebvre, Executive Director and Chief Executive Officer</p>		
<p>Ontario Ministry of Community Safety and Correctional Services Andrew McCallum, Regional Supervising Coroner for Eastern Ontario, Office of the Chief Coroner</p>		
<p>Best Medicines Coalition Gail Attara, Member, Steering Committee Linda Wilhelm, Vice-Chair, Operations Committee</p>	2008/03/06	16
<p>Canadian Health Coalition Michèle Brill-Edwards, Board Member</p>		

Organizations and Individuals	Date	Meeting
Drug Safety Canada Terence Young, Chair	2008/03/06	16
Cancer Advocacy Coalition of Canada James Gowing, Chair of the Board William Hryniuk, Past Chair	2008/03/11	17
Expert Advisory Committee on the Vigilance of Health Products Diane Brideau-Laughlin, Chair		
Institute for Safe Medication Practices Canada Sylvia Hyland, Vice President		
Université de Montréal Yola Moride, Associate Professor, Faculty of Pharmacy		
Anemia Institute for Research and Education Durhane Wong-Rieger, President and Chief Executive Officer	2008/03/13	18
Consumers' Association of Canada Mel Fruitman, Vice-President		
PharmaWatch Colleen Fuller, President Carol Kushner, Director		
Canadian Women's Health Network Madeline Boscoe, Executive Director	2008/04/01	19
University of British Columbia Bruce Carleton, Senior Clinician Scientist, Child and Family Research Institute, BC Children's Hospital		
As an individual Patrick Orr, Lawyer	2008/04/08	21
St. Michael's Hospital Andreas Laupacis, Executive Director, Li Ka Shing Knowledge Institute		
University of British Columbia Steve Morgan, Assistant Professor, Centre for Health Services and Policy Research		

Organizations and Individuals	Date	Meeting
<p>Canada Health Infoway Richard Alvarez, President and Chief Executive Officer Mike Sheridan, Chief Operating Officer</p> <p>Office of the Auditor General of Canada Sheila Fraser, Auditor General of Canada Neil Maxwell, Assistant Auditor General</p> <p>Office of the Privacy Commissioner of Canada Patricia Kosseim, General Counsel Jennifer Stoddart, Privacy Commissioner</p>	2008/04/10	22
<p>McGill University Robyn Tamblyn, Scientific Director, Clinical and Health Informatics Research, Department of Medicine</p> <p>University of Victoria Alan Cassels, Pharmaceutical Policy Researcher, School of Health Information Sciences</p> <p>York University Mary Wiktorowicz, Chair and Associate Professor, School of Health Policy and Management</p>	2008/04/15	23
<p>As individuals Julie-Kim Godin, Attorney, Ménard, Martin, Avocats</p> <p>Jean-Pierre Ménard, Attorney and Specialist in Medical Law, Ménard, Martin, Avocats</p> <p>Brogan Inc. Tom Brogan, President and Chief Executive Officer</p> <p>U.S. Food and Drug Administration Gerald Dal Pan, Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research</p>	2008/04/29	25

Organizations and Individuals	Date	Meeting
<p>Department of Health</p> <p>Marc Berthiaume, Director, Marketed Pharmaceuticals and Medical Devices Bureau, Marketed Health Products Directorate, Health Products and Food Branch</p> <p>David Clapin, Branch Science Advisor, Office of Science and Risk Management, Health Products and Food Branch</p> <p>David K. Lee, Director, Office of Patented Medicines and Liaison, Therapeutic Products Directorate</p> <p>Michael Vandergrift, Director General, Policy, Planning and International Affairs Directorate, Health Products and Food Branch</p> <p>Ontario Ministry of Health and Long-Term Care</p> <p>Brent Fraser, Director, Drug Program Services Branch</p> <p>Public Health Agency of Canada</p> <p>Barbara Law, Interim Director, Vaccine Preventable Diseases Prevention and Vaccine Safety</p> <p>University of British Columbia</p> <p>Bruce Carleton, Senior Clinician Scientist, Child and Family Research Institute, BC Children's Hospital</p>	2008/05/01	26

APPENDIX B LIST OF BRIEFS

Organizations and Individuals

Anemia Institute for Research and Education

Best Medicines Coalition

BIOTECanada

Brogan Inc.

Canada Health Infoway

Canada's Research-Based Pharmaceutical Companies (Rx & D)

Canadian Generic Pharmaceutical Association

Canadian Institute for Health Information

Canadian Medical Association

Canadian Men in Nursing Group

Canadian Pharmacists Association

Canadian Society of Hospital Pharmacists

Canadian Women's Health Network

Cancer Advocacy Coalition of Canada

Consumers' Association of Canada

Drug Safety Canada

Federation of Medical Regulatory Authorities of Canada

Lexhin, Joel

National Association of Pharmacy Regulatory Authorities

NDMAC

Orr, Patrick

Organizations and Individuals

PharmaWatch

St. Michael's Hospital

University of British Columbia

University of Victoria

Women and Health Protection

York University

REQUEST FOR GOVERNMENT RESPONSE

Pursuant to Standing Order 109, the Committee requests that the government table a comprehensive response to this Report.

A copy of the relevant Minutes of Proceedings ([Meetings Nos. 9, 10, 11, 13, 14, 16, 17, 18, 19, 21, 22, 23, 25, 26, 33, 36 and 37](#)) is tabled.

Respectfully submitted,

Joy Smith, MP
Chair

**Bloc Québécois – Supplementary Opinion
Report of the Standing Committee on Health
Post-Market Surveillance of Pharmaceuticals**

The Bloc Québécois would like first of all to acknowledge the invaluable contribution made by the stakeholders and witnesses who took part in the study on the post-market surveillance of pharmaceuticals.

In response to the Standing Committee on Health's report, which was the outcome of a study begun in January 2008 and concluded on June 17, 2008, the Bloc Québécois would like to voice reservations about some of the recommendations. These reservations were discussed in committee but were not incorporated into the report, and the Bloc Québécois would like to emphasize them by taking advantage of the right to attach a supplementary opinion to the report.

❖ **THE IMPORTANCE OF REAFFIRMING QUEBEC AND PROVINCIAL JURISDICTION OVER HEALTH**

A. Training of health professionals and professional regulatory bodies

The report refers repeatedly to the training of health professionals. But such training, the education of health professionals, falls within the jurisdiction of Quebec and the provinces. Recommendation 2 does mention this fact, but in our opinion it should be reiterated every time a reference is made to the training of health professionals (notably in recommendations 2 and 16).

It should also be pointed out that Health Canada has no authority to require health professionals or professional regulatory bodies to report adverse drug reactions: professional regulatory bodies are governed by Quebec and provincial legislation. It is our opinion that Recommendation 6, which calls for "funding for technological tools required to increase reporting by health professionals (physicians, pharmacists, nurses, etc.) in their daily practices", should make this fact explicit.

With respect to these two aspects (training and duties of health professionals / management of professional regulatory bodies), a recommendation proposed by the Bloc Québécois should be noted:

BLOC QUÉBÉCOIS RECOMMENDATION

- That the optimal use of resources on the ground be encouraged with respect to post-market surveillance, while taking into account the fact that professional regulatory bodies fall under Quebec and provincial jurisdiction, that Health Canada cannot impose on any professional regulatory body a duty involving post-market follow-up, and that the training of health professionals is an educational matter, with education a jurisdiction exclusive to Quebec and the provinces.

B. Medical records management and e-prescribing

Bearing in mind that adequate post-market surveillance must be ensured while at the same time Quebec and provincial jurisdiction must be reaffirmed, the Bloc Québécois has certain concerns about Recommendation 15, which refers to additional investment in Health Canada's Infoway and in e-prescribing.

Quebec is currently developing its own system for computerising medical records, an initiative that falls within its area of jurisdiction. Quebec's *Act respecting Health and Social Services* and its *Professional Code* already regulate the management of medical records¹ and the terms and conditions for the prescribing of pharmaceutical products.² The actions proposed by the Committee would be nothing but duplication.

We would have preferred Recommendation 15 to recognize that Quebec has the right to opt out with full and unconditional financial compensation for any investment having to do with Health Canada's Infoway and the e-prescription system, but our amendment was rejected in committee.

❖ RESPECT FOR EXISTING STRUCTURES IN QUEBEC

With regard to the reporting of adverse drug reactions, Quebec already has, in each of its health-care institutions, risk and quality management committees to which must be reported any care-related incident, including adverse drug reactions.

Though paragraphs 95 and 96 of the report refer to the existence of such structures, in Quebec in particular, at no time – as a witness from Quebec pointed out – is any mention made of the necessity of not duplicating existing structures should the reporting of adverse drug reactions become mandatory for hospitals.

It should also be made explicit that any mandatory reporting of adverse reactions by hospitals would be contingent upon the Government of Canada's obtaining the consent of Quebec and the provinces, given that hospital management falls within their jurisdiction. This being so, the report's Recommendation 3 should have spelled out that Quebec and the provinces have jurisdiction.

The Bloc Québécois made two recommendations along these lines:

BLOC QUÉBÉCOIS RECOMMENDATION

- That the federal government recognize that Quebec has been proactive in this area, having adopted legislation on the safe provision of health services in 2002,

¹ Under section 505, paragraph 24, of the Act, the Government of Quebec may by regulation “determine standards governing the compilation and keeping of users’ records, the particulars and documents they contain and their use, communication and, subject to section 520.3.2, storage and destruction”.

² Under section 39.3 of the Code, “the word ‘prescription’ means a direction given to a professional by a physician, a dentist or another professional authorized by law, specifying the medications, treatments, examinations or other forms of care to be provided to a person or a group of persons, the circumstances in which they may be provided and the possible contraindications. A prescription may be individual or collective.”

that it take into account existing structures, and that it avoid all pointless and expensive duplication in its future initiatives involving post-market surveillance of pharmaceuticals.

BLOC QUÉBÉCOIS RECOMMENDATION

- That, if provisions were introduced to make the reporting of adverse reactions mandatory by health-care institutions and hospital employees, this would not apply to health-care institutions in Quebec because they come within provincial jurisdiction, and that the “Quebec clause” be taken into account.

❖ RESEARCH INTO DRUG SAFETY AND EFFECTIVENESS: THE IMPORTANCE OF PHARMACOEPIDEMIOLOGICAL STUDIES

Although Recommendation 10 speaks of the importance of multidisciplinary research into pharmaceutical safety and of incorporating pharmacoepidemiology into such research, it is our opinion that the Committee's recommendations could have been more far-reaching when it comes to pharmacoepidemiology. They could have reflected the suggestions of some witnesses that conducting such studies should be mandatory once a pharmaceutical comes on the market.

The Bloc Québécois made the following recommendation in this regard:

BLOC QUÉBÉCOIS RECOMMENDATION

- That the government consider passing legislation making it mandatory to conduct pharmacoepidemiological studies when a drug comes on the market, to ensure that real-life safety data will be generated as rapidly as possible and communicated to regulatory bodies.

❖ REGULATORY RESOURCES: CONSIDERING THE POSSIBILITY OF SETTING UP AN INDEPENDENT INVESTIGATIVE BODY

A number of witnesses stressed the importance of drawing a clear line between the authorities that approve pharmaceuticals and those that do post-market follow-up. Health Canada has set up a separate unit within its Health Products and Food Branch to carry out post-market surveillance: the Marketed Health Products Directorate.

But these are not two separate and independent bodies. A number of witnesses argued, moreover, that there was a risk of an apparent conflict of interest, given that the same entity is responsible for both approval and surveillance of pharmaceuticals.

Although the Committee reiterates in one of its recommendations the importance of Health Canada's making a greater distinction and differentiation between the authorities responsible for approving pharmaceuticals and for monitoring them (as regards both mechanisms and funding), we think more is needed. Consideration should be given to setting up an independent body that would be responsible for investigating incidents related to pharmaceuticals, as some witnesses suggested. This independent body could, like the Transportation Agency, report direct to Parliament through the Queen's Privy Council.

NDP Supplementary Report to the Standing Committee on Health's study of the Post-Market Surveillance of Pharmaceuticals, June 2008 by Judy Wasylycia-Leis, MP

In our study of post-market surveillance, the Committee was presented with a rare consensus among the many witnesses that appeared before us: our current approach to drug safety is in trouble. Canadians share this feeling and want and deserve a drug safety system that ensures, based on the best scientific evidence available, that the therapeutic drug products on the market are safe to use. Why should Canadians expect any less? Instead, we are confronted with a constant barrage of warnings and recalls – not about drugs that have been tampered with or that have been misused, but that through their approved use are causing harm to health and in some cases costing lives. Properly prescribed drugs following government-approved manufacturer instructions are estimated to be the 4th ranking cause of death in North America. A recent study found that one of every nine visits to a Canadian emergency room is caused by medication problems – of which 39% are due to drug side-effects, including pain, bleeding, rashes, and hallucinations.

Hazardous drugs continue to gain market access. We were reminded of the more serious cases like COX-2 inhibitors with trade names like Celebrex and Vioxx with its hundreds of thousands of heart attacks and many thousands of deaths. Prepulsid, Evra patch, zelnorm, Heparin – the list goes on. And then there are countless others that never make the headlines. And that, in itself, is part of the problem. Our existing post-market surveillance system picks up less than 10% of the adverse drug reactions that occur. Statistics cannot begin to describe the pain and suffering caused to victims of serious reactions and their loved ones. Simply including a long list of things we, as consumers, should look out for in miniscule print on the label or inside the package is not an acceptable answer.

Meanwhile, Canadians spent \$27 billion on drugs last year and there is considerable pressure by pharmaceutical manufacturers to increase that spending and the profits it brings as quickly as possible.

How we got here

We find ourselves in this desperate state not as the result of some single cataclysmic mistake. We have arrived here at the end of a 30-year journey where government after government has caved in and put public health protection at risk to further a corporate pharmaceutical agenda. Along the way, it has reduced Health Canada's capacity to independently ensure drug safety and created a departmental culture in which accommodating pharmaceutical 'clients' is the highest value – even overriding public safety.

The de-professionalization of departmental scientific staff in the 1970s and 80s, fanned by 'cut red tape' rhetoric, escalated with the record Liberal financial cutbacks of the mid-90s and the conversion of the regulatory relationship into a 'partnership' with the pharmaceutical corporations. This was followed quickly by the dismantling of the drug research labs in 1997 over NDP objections and the later introduction of strict new departmental deadlines for completing drug approvals to ensure speedy company access to markets.

Paralleling the operational shift at Health Canada were repeated government efforts to "rationalize" the legal framework to remove liability and lessen departmental responsibility for Canadians' safety: in the Health Protection Business Enterprise, in 1995-6; the Health Protection Branch Transition (*Shared Responsibilities, Shared Vision*), in 1998; Bill C-80, the *Canada Food Safety and Inspection Act*, in 1999; Health & Safety First – A Proposal to Renew Federal Health Protection Legislation (*Safety*

First), in 2003; and in 2006, the Blueprint for Renewing Canada's Health Products & Regulatory System (*Blueprint for Renewal*).

Today, we find ourselves facing yet another round with Bill C-51, a bill that overlaps many of the issues examined in this study. Central to this latest proposal is “progressive licencing”, a cause of concern to many witnesses who fear the government's approach to life cycle monitoring will result in a relaxation of pre-market rigour and the increased use of conditional approvals. In the words of the Department, “*shifting the focus* from pre-market review to one that continuously assesses a product's risks and benefits, both before and after it reaches the market, by putting conditions on the licence”. Again, speedier approvals to pave the way for corporate profits.

What's the problem?

Our drug safety system is a continuum from pre-market trials through post-market use. To assess post-market surveillance, therefore, we must also take into account the strengths and weaknesses of the pre-approval process.

Witnesses drew our attention to a number of serious weaknesses in our current pre-market system, including the lack of transparency in drug trials that is somehow excused by the government on commercial, proprietary grounds. Despite greater openness elsewhere, in Canada commercial interests trump consumer and public interest. Other weaknesses of concern to witnesses included:

- the manipulation or incomplete reporting of clinical trials by drug companies, as described in the *Journal of the American Medical Association* revelations concerning Vioxx in April;
- that the use of rigid trial completion deadlines may result in premature and potentially harmful approval decisions evidenced through an increase in adverse reactions, as described in the March issue of the *New England Journal of Medicine*;
- efficacy questions from the lack of head-to-head comparisons and the estimation by the US Food and Drug Administration that 80% of “new drugs” entering the market are “me-too” drugs offering no improvement over drugs that are already available;
- the exclusion of non-therapeutic ingredients; and
- the lack of a registry to track all trials, once started.

Weaknesses at the post-market end of the continuum were also pointed out. One of the oft-heard criticisms was that our system is passive and does not provide pro-active surveillance, waiting for trouble to emerge. One obvious aspect of that passivity is Health Canada's over-reliance on the American FDA to initiate warnings and recalls. Heparin provides a recent example. Other weaknesses include:

- the need for more human resources within Health Canada for both pre- and post-market surveillance – a situation made worse by the internal competition for those inadequate resources between pre- and post-market monitors — not to mention other departmental areas;
- the lack of a mechanism to address the dangers of off-label prescribing (Health Canada's inability to pursue additional approvals for new applications of drugs — a power reserved for the original marketing firm;
- the lack of post-market standards;
- in relation to adverse reaction reporting:
 - the low reporting rate of only about 10% of serious, unexpected incidents;
 - no uniform quality standard;
 - inadequate analytical capacity;

- no timeframe for action or even the requirement of feedback;
- the lack of public and professional awareness and training in submitting reports;
- poor communication — the presentation of information, such as it is, is not easily understood;
- the need for greater integration with the Common Drug Review and national formulary process; and
- the slow progress on electronic records and the urgent need for the integration of systems across jurisdictions and the integration of drug registries, health outcomes and patient records.

Conclusion and Recommendations

The post-market surveillance of drugs is an important responsibility of the government. Finding solutions to the many weaknesses that have developed in our drug safety program is as complex as the problems themselves. The following recommendations provide direction to improving drug safety for all Canadians based on testimony before the Committee. It should be noted, however, that the success of these recommendations, or others, depends on a change in the culture within Health Canada that reasserts the dominance of the precautionary principle and public safety together with the government's provision of additional financial and human resources to fully implement a pro-active drug safety strategy. We therefore recommend that the government:

- Reassert the predominance of the precautionary principle as the philosophical cornerstone and practical guide in the regulation of drug safety;
- Increase transparency throughout the drug safety regime ensuring that the public, health professionals and regulators have access to information that will impact on their health. For example, by:
 - setting up a web site with postings of all pre-approval clinical trials and a summary & rationale of each decision,
 - requiring all protocols and results of clinical trials – including those not completed – to be provided to the government regulator,
 - requiring all suspected adverse reaction reports and the protocol and results of post-market safety evaluations to be made public;
- End its 'partnership' relationship with the pharmaceutical industry and return to its mission of health protection. For example, it should dispense with its system of deadlines for pre-market approvals in all but clearly specified circumstances such as breakthrough drugs and the treatment of terminal conditions;
- Provide budgetary and human resources adequate to fully conduct its health protection responsibilities for drugs, including the pro-active post-market surveillance of approved drugs (Post-market surveillance is a public responsibility and its design and administration can not be left to manufacturers' risk management planning with its inherent conflict of interest.);
- Establish an independent oversight regulatory safety board, separate from the regulator, to investigate problems arising after approvals;
- Actively support the accelerated development of the National Pharmaceutical Strategy's Drug Effectiveness and Safety Network as an independent tool for the post-market regulation of drugs;

- Increase support for the Canada Infoway and the integration of electronic health records into the post-market surveillance of drugs and adverse reactions in a national tracking system modeled on the British Columbia's PharmaNet data system;
- Vigorously maintain support for the Common Drug Review, and CADTH;
- Tighten and enforce restrictions against direct-to-consumer advertising of drugs, as recommended by the Committee in *Opening the Medicine Cabinet*;
- Require that gender analysis be included in all pre- and post-market safety assessments of drugs;
- Improve adverse drug reaction reporting and response through, for example:
 - enforcing the existing mandatory requirement for the pharmaceutical industry to report serious adverse drug reactions, and that this reporting encompass all suspected adverse effects they become aware of, including within clinical trials and events reported outside of Canada
 - making public periodic safety update reports
 - providing financial support for the specialized training of additional ADR analysts
 - increasing the education of both the public & health professionals about ADR reporting
 - introducing the use of a Black Triangle or other easily-recognizable symbol indicting the need for attention to adverse reaction potential
 - including the reporting of the impact of adverse drug reactions in population health statistics, for example from hospital and coroner data
 - evaluating the effectiveness of warnings
 - designating deadlines for responses to ADR reports
 - providing timely feedback to the originators of ADR reports.

In addition, the government needs the authority to require post-marketing studies and to initiate testing for additional uses of approved drugs.