

March 2013



# PRESCRIPTION PHARMACEUTICALS IN CANADA:

*Post-Approval Monitoring of Safety and Effectiveness*

Standing Senate Committee on Social Affairs,  
Science and Technology

The Honourable Kelvin K. Ogilvie, *Chair*

The Honourable Art Eggleton, P.C., *Deputy Chair*





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## ORDER OF REFERENCE

Extract from the *Journals of the Senate*, Tuesday, November 22, 2011:

*The Honourable Senator Ogilvie moved, seconded by the Honourable Senator Frum:*

*That the Senate Standing Committee on Social Affairs, Science and Technology be authorized to examine and report on prescription pharmaceuticals in Canada, including but not limited to:*

- (a) the process to approve prescription pharmaceuticals with a particular focus on clinical trials;*
- (b) the post-approval monitoring of prescription pharmaceuticals;*
- (c) the off-label use of prescription pharmaceuticals; and*
- (d) the nature of unintended consequences in the use of prescription pharmaceuticals.*

*That the committee submit its final report no later than December 31, 2013, and that the committee retain until March 31, 2014, all powers necessary to publicize its findings.*

*The question being put on the motion, it was adopted.*

Gary W. O'Brien  
*Clerk of the Senate*

## MEMBERS

The Honourable Kelvin Kenneth Ogilvie, *Chair*  
The Honourable Art Eggleton, P.C., *Deputy Chair*

### The Honourable Senators:

Jane Cordy, Lillian Eva Dyck, Nicole Eaton,  
Tobias Enverga, Yonah Martin, Jim Munson  
Judith Seidman, Asha Seth, Josée Verner, P.C.

### Ex Officio Members:

The Honourable Senators Marjory LeBreton, P.C.  
(or Claude Carrigan) and James Cowan  
(or Claudette Tardif).

### Other Senators who have participated from time to time in the study:

The Honourable Senators Ataullahjan, Callbeck,  
Chaput, Demers, Doyle, McInnis, Mercer, Moore,  
Neufeld and Raine.

### Parliamentary Information and Research Services, Library of Parliament:

Sonya Norris, Analyst.

### Clerk of the Committee:

Jessica Richardson.

### Senate Committees Directorate:

Diane McMartin, Administrative Assistant.





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# EXECUTIVE SUMMARY

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## INTRODUCTION

On November 22, 2011, the Senate adopted an Order of Reference authorizing the Standing Senate Committee on Social Affairs, Science and Technology to examine and report on prescription pharmaceuticals in Canada. The study includes four components, each to be studied separately, which are: the process to approve prescription pharmaceuticals with a particular focus on clinical trials; the post-approval monitoring of prescription pharmaceuticals; the off-label use of prescription pharmaceuticals; and, the nature of unintended consequences in the use of prescription pharmaceuticals.

This report is on the second phase of the study, for which the committee heard from witnesses between October 3 and November 21, 2012. Over the course of eight meetings, the committee heard testimony from Health Canada and Office of the Auditor General of Canada officials, representatives from the pharmaceutical industry, patient advocates, medical, ethical and legal academics and finally, representatives of national organizations concerned with pharmaceutical policy.

## ISSUES OF CONCERN

The report *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* (the Clinical Trials Report) from the first phase of this committee's study on prescription pharmaceuticals discussed the issue of clinical testing of investigational drugs to assess their safety and efficacy. While the pre-approval assessment of safety and efficacy is critical and the clinical trials necessary for the assessment must be optimized, it is generally acknowledged that the safety and effectiveness profile of every new drug continues to evolve once it is used in the general population.

Health Canada is responsible for monitoring this 'real-world effectiveness' of pharmaceuticals after they are granted market approval.

Traditionally, Health Canada has relied on reports of adverse drug reactions (ADRs) to identify safety signals and issue necessary advisories or warnings. ADR reporting, while mandatory for drug manufacturers when they are made aware of any, is voluntary for health professionals and the public. Although the number of ADR reports submitted to Health Canada has increased, this information still reflects only a small proportion of the actual ADRs experienced by the general population. Recently, the Drug Safety and Effectiveness Network (DSEN) was created within the Canadian Institutes of Health Research to carry out additional research on potential safety signals identified by Health Canada.

Health Canada has acknowledged the need to adopt a life-cycle approach to drug regulation and indicated to this committee that regulatory modernization is a departmental priority. The creation of DSEN helps to move post-approval monitoring from the traditional approach of relying on ADR reports to a more active surveillance model. However, the committee is concerned that Canada is neither keeping pace with international requirements nor following the legislative, regulatory and policy models in other jurisdictions in order to optimize the post-approval monitoring of prescription drugs in Canada.

In response, this report makes 19 recommendations that address issues such as: legislative and regulatory reform; the independence and effectiveness of DSEN; DSEN's research model; data collection through electronic health records; ADR reporting; post-approval strategies for population sub-groups; communication strategies;



and, implementing the necessary changes in response to the 2011 Auditor General report on regulating pharmaceuticals.

In terms of legislative and regulatory reform, the committee was told by almost all witnesses that Canada's *Food and Drugs Act* is outdated and in need of modernization. Consistent with the committee's observations in the Clinical Trials Report that modernization is essential to Canada's management of pharmaceuticals, the committee recommends additional elements of pharmaceutical policy that must be implemented. In this regard the committee is calling on the Minister of Health to introduce drug legislation that provides additional authorities to the federal government. As well, regulatory reform must accompany a modernized legislative framework. The committee is encouraged by Health Canada's repeated commitment to regulatory reform but notes that the department has indicated its intention for such an update for several years. Therefore the committee is calling on the Minister of Health to implement comprehensive regulatory reform which applies a life-cycle approach to drug management, including long-term studies of drug safety, beginning in 2013. The committee further specifies that the new approach to drug regulation must ensure that funding of post-approval activities is increased such that pre- and post-approval activities are equally funded by the department.

Although the committee heard considerable support for the recently created DSEN, it also heard concern from several witnesses about whether DSEN is sufficiently removed from the influence of the pharmaceutical industry, since CIHR promotes collaboration with the industry. The committee encourages DSEN in its work but would like measures taken to ensure its independence as well as its sustainability. These measures include: an assessment of its work and analysis of its ability to operate independently; a commitment

by the federal government for sustained funding; budgetary independence from CIHR; and creation of a mechanism to review DSEN findings and, where relevant, monitor the actions taken by Health Canada in response to those findings.

Also in regard to DSEN, the committee notes the support among many witnesses for its organizational structure, but agrees with those who suggested that the research model currently used by DSEN could be further enhanced. As such, the committee suggests that DSEN could be used as a means to apply active reporting of ADRs. The committee urges the creation of clinical models that encourage active monitoring of ADRs with dedicated resources for filing reports with Health Canada. In this regard, it sees a further role for the research network capacity recommended in the Clinical Trials Report in active post-approval surveillance.

The electronic health record (EHR) was described by several witnesses as an effective means of improving the quality and quantity of ADR reports, which in turn improves the capacity for Health Canada and DSEN to assess potential safety issues. One aspect of a comprehensive EHR is data regarding dispensed prescriptions and the committee notes the success of British Columbia's PharmaNet in this regard. The committee recommends that the Minister of Health discuss implementing similar systems with provincial and territorial counterparts. Further, the committee urges compatibility and linkability of dispensed prescription drug databases with patient electronic medical records (EMRs) and EHRs. Finally, the committee would like ADR reporting facilitated by linking the electronic ADR form through patient EMRs and EHRs.

With respect to specific sub-groups of the population such as children, pregnant and nursing women and the elderly, the committee emphasises that there should not be a lower threshold of drug safety and effectiveness. Similar



to the concerns raised by this committee in the Clinical Trials Report, post-approval monitoring of prescription drugs must be strengthened in order to protect these sub-groups. Consistent with the committee's recommendation at that time that more clinical trials include specific sub-groups, but acknowledging that additional information will need to be collected post-approval, the committee would like to see post-approval studies and systematic safety reviews in relevant sub-groups of the population. Finally, the committee notes that research conducted within DSEN in response to queries submitted by Health Canada or other stakeholders may result in identification of issues among these populations. It recommends that such secondary findings be considered for follow up studies.

Witnesses spoke of the need to improve and standardize the information being provided to those consuming the drugs. The committee agrees with concerns raised that the information provided to patients at the point of sale is not necessarily approved by Health Canada. The department should implement standardized Patient Information Leaflets (PILs) and prohibit the sale of any prescription drug unless accompanied by its PIL. The proposed PIL should also include information about the Health Canada website and phone number to which ADRs can be reported.

Witnesses also spoke of the need to improve communication about new drugs, and drugs with potential safety concerns, through labelling. In this regard the committee is recommending that Health Canada adopt the labelling requirements that have been implemented in the United States and the United Kingdom, which identify new products, a category of drug with a higher incidence of ADRs, as well as drugs that are linked to serious side effects. Implementation of this recommendation should help to encourage ADR reporting. Health Canada should also become more transparent in its identification of potential safety signals. The

committee recommends that Health Canada provide information about the Risk Management Plans that have been submitted by drug manufacturers, the safety signals that have been identified, the status of subsequent assessments and the drugs for which manufacturers must conduct post-approval studies, including long-term follow-up.

Finally, the committee notes the Fall 2011 report of the Auditor General of Canada on the regulation of pharmaceuticals. The committee would like Health Canada to provide assurance that it has implemented all necessary changes in response to that report.

## CONCLUSION

The committee acknowledges that Health Canada has improved its approach to post-approval monitoring of prescription pharmaceuticals in recent years. The department has implemented promising initiatives such as the Drug Safety and Effectiveness Network and has worked to improve efficiencies of post-approval monitoring activities within the Marketed Health Products Branch of Health Canada. However, there is still work to be done in its management of prescription pharmaceuticals. Health Canada and the Drug Safety and Effectiveness Network must continue their efforts in this regard. The committee would like to see this report's recommendations implemented quickly to improve the safety of prescription drugs, to increase transparency in their management, and to foster trust among Canadians in our drug regulatory regime.





# 1. INTRODUCTION

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The Senate Standing Committee on Social Affairs, Science and Technology is undertaking a four phase study on prescription pharmaceuticals, as described in the Order of Reference adopted on November 22, 2011. On November 1, 2012 it tabled a report on the first phase of the study on clinical trials entitled *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* (the Clinical Trials Report). Between October 3 and November 21, 2012, the committee heard from witnesses in regard to the second phase of this study, the post-approval monitoring of pharmaceuticals.

Over the course of eight meetings, the committee heard testimony from officials from Health Canada and the Canadian Institutes of Health Research as well as the Office of the Auditor General of Canada, representatives from the pharmaceutical industry, patient advocates, medical, ethical and legal academics and finally, representatives from national organizations concerned with pharmaceutical policy.





## 2. CONTEXT – THE DRUG APPROVAL PROCESS

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### A. HEALTH CANADA'S RESPONSIBILITY FOR DRUG REGULATION

As described in the Clinical Trials Report, all pharmaceuticals, or drugs, must be approved by Health Canada before they can be marketed in this country. *The Food and Drugs Act* (the Act) defines “drug” as:

Any substance or mixture of substances manufactured, sold or represented for use in:

- a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- b) restoring, correcting or modifying organic functions in human beings or animals, or
- c) disinfection in premises in which food is manufactured, prepared or kept.<sup>1</sup>

Health Canada categorizes drugs for human use as prescription drugs, non-prescription drugs, radiopharmaceuticals, and biologics.<sup>2</sup> The following sections describing Health Canada’s role in pharmaceutical regulation are derived from the Clinical Trial Report and are reiterated to provide the context necessary for this phase of the study.

### B. OVERVIEW OF DRUG APPROVAL WITHIN HEALTH CANADA

All regulatory and enforcement activities, and most policy activities, associated with pharmaceuticals are conducted within the Health Products and Food Branch (HPFB) of Health Canada. Directorates

within HPFB include one each for food and veterinary drugs and four for drugs, namely; the Biologics and Genetic Therapies Directorate (BGTD), the Marketed Health Products Directorate (MHPD), the Natural Health Products Directorate (NHPD) and the Therapeutic Products Directorate (TPD). HPFB also includes an Inspectorate which is responsible for compliance and enforcement activities associated with drugs and medical devices.

Reviews of prescription drug submissions are carried out within the following four bureaus of TPD depending on the type of drug being reviewed: the Bureau of Cardiology, Allergy and Neurological Sciences; the Bureau of Gastroenterology, Infection and Viral Diseases; the Bureau of Metabolism, Oncology and Reproductive Sciences; and the Bureau of Pharmaceutical Sciences. The drug approval process follows the steps laid out below for new drugs, with some modifications allowed for other categories of drugs.

#### i. Clinical Trials of New Drugs

Clinical trials are conducted in human subjects to test the safety and efficacy of newly developed drugs that have shown positive results in pre-clinical investigation. Testing in humans is conducted in three or four phases:

Phase I – Involves a small number of healthy subjects to test the toxicity, absorption, distribution and metabolism of the drug.

Phase II – Involves trials with a larger set of individuals suffering from the condition for which the drug was developed, to test efficacy and safety.

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<sup>1</sup> *Food and Drugs Act*, section 2.

<sup>2</sup> Please refer to the Standing Senate Committee on Social Affairs, Science and Technology’s report on the first phase of the study entitled *Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* for more detail. The report is available at <http://www.parl.gc.ca/Content/SEN/Committee/411/soci/DPK/01nov12/reports-e.htm>



Phase III – Involves a greater number of people also with the condition in question, to test the drug's performance in relation to a placebo and/or standard therapy.

Phase IV – Involves all studies conducted after a drug has received approval that were not considered necessary for approval but are often important for optimizing the drug's use, also referred to as post-market or post-approval studies.

These trials are subject to the clinical trial regulations under Part C, Division 5 of the *Food and Drug Regulations* (the Regulations) which seek to ensure: the safety of the participants; the integrity of the study; the validity of the data; and strict controls over the use of an unapproved drug. Authorization to conduct phase I, II, or III clinical trials must be obtained from Health Canada before starting the investigation. Phase IV clinical trials do not require authorization.

## ii. Approval Process for New Drugs

### a. Pre-submission Meeting

Once the developer and/or manufacturer of a new investigational drug is confident that it has produced a compound that can successfully gain Health Canada's approval, a pre-submission meeting is encouraged by TPD, but is not essential. This meeting can be beneficial to the drug sponsor as well as Health Canada as it alerts the regulator to upcoming submissions and allows the sponsor an opportunity to optimize their submission package.

### b. Submission Filing

This is the first step in the drug approval process. Submission filing involves submitting to TPD a New Drug Submission, or NDS. The NDS must contain information that: describes the drug; asserts its quality; summarizes the investigational studies and clinical trials pertaining to the drug

including adverse reactions observed during clinical trials; and finally, includes raw data from pre-clinical studies.

### c. Screening

When TPD receives an NDS, it first screens the package to ensure that the submission is complete and in the proper format. Health Canada aims to meet a target of 45 calendar days for screening NDSs. Upon a successful screening, the submission proceeds to the technical review. If, however, deficiencies are identified in the submission filing, the sponsor is sent a screening deficiency notice to which it has 45 calendar days to respond and address the noted deficiencies. Unsuccessful candidates are sent a Screening Rejection Letter.

### d. Technical Review

Upon successful completion of the screening process, the submission passes to the technical review component. TPD has established a target of 300 days for this phase of the drug approval process. Evaluation of the submission involves a detailed review of all the material submitted in the filing in order to produce a comprehensive analysis of the quality, safety and efficacy of the candidate drug and ensures that the risks associated with taking the drug do not outweigh the benefits. Clinical trial data is central to determining the safety/efficacy profile for a candidate drug. At any point during the review TPD can request clarification, re-evaluation or expansion of the submitted material.

Possible outcomes of the technical review are:

- A Notice of Deficiency if the submission is incomplete, at which point the review process stops but can resume if the deficiencies are addressed;
- A Notice of Deficiency-Withdrawal letter if the applicant does not satisfactorily address deficiencies;



- A Notice of Non-compliance if TPD finds that the submission is incomplete or deficient which lists all deficient or incomplete aspects of the submission, to which the applicant can respond;
- A Notice of Non-compliance-Withdrawal letter if the applicant does not respond or if the response is unacceptable at which time the submission will be considered withdrawn;<sup>3</sup>
- A Notice of Compliance (NOC) which certifies that the drug complies with all requirements of the Act and its regulations. At this time a Drug Identification Number (DIN), an eight digit number, is also issued which authorizes the drug to be marketed in Canada;<sup>4</sup> or,
- A Notice of Decision and a Summary Basis of Decision for each approved drug outlining its risk-benefit analysis which are posted on Health Canada's website.

When TPD issues a NOC for a new drug, the approval extends only as far as the specifics for which the manufacturer initially requested approval. The dosing information, route of administration, labelling, formulation, method of manufacture and indications for use are specified in the NOC and any deviation from these parameters requires a new approval, in which case the manufacturer must file a Supplemental New Drug Submission.



### iii. Variations of the Approval Process for Certain Categories of New Drugs

Under certain specified conditions, the approval of drugs can be reduced from the standard 300 day review. Submissions for generic versions of new drugs, for example, include material similar to that required for a NDS except that there is not the same requirement for clinical trials since a pharmaceutically equivalent product is already on the market. Instead, there is a focus on bioavailability as well as chemistry and manufacturing information to ensure the quality and equivalence of the drug. The target review time for generic drug submissions, called abbreviated new drug submissions, is 180 days.

Health Canada also provides two options for expedited review of drugs for serious and life-threatening conditions. First, priority review of a submission may be granted for drugs that are intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions for which there is either no product currently marketed in Canada or the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is better than that of existing therapies. Priority reviews are subject to the same requirements as NDSs, including clinical trial data, but are processed more quickly, whereby the target for screening is reduced to 25 days and the target for the review is 180 days.

The second process for expedited review allows for a reduced threshold of evidence than that required under the NDS process, that is, that the amount of clinical trial evidence may be reduced. Under this category of drug review Health Canada can issue a NOC with Conditions (NOC/c) which requires that the manufacturer continue to collect data on the drug's safety and effectiveness, essentially supplementing the clinical trial evidence base to bring it up to the standards required for NDSs.

<sup>3</sup> Sponsors issued rejection letters or notices of non-compliance or deficiency can submit Requests for Reconsideration to TPD.

<sup>4</sup> The DIN identifies: manufacturer; product name; active ingredient(s); strength(s) of active ingredient(s); pharmaceutical form; and, route of administration.



Similar to priority review, the NOC/c process can be applied to drugs for serious and life-threatening conditions where there is either no product currently marketed in Canada or the new product represents a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is better than that of existing therapies. This process allows for a screening target of 25 days and a review target of 200 days.

There is the possibility that new drugs may be approved by Health Canada when the safety, efficacy and quality data on them is limited. Under extraordinary circumstances a drug may be given market authorization with less information from clinical trials than would normally be permitted. These circumstances include emergencies such as exposure to a chemical, biological, radiological or nuclear substance which requires action to treat or prevent the resulting condition. The nature of these circumstances makes it impossible to design and conduct controlled clinical trials to first test the new drug. Therefore, Health Canada's Extraordinary Use New Drug policy allows approval of these drugs with little or no clinical trial data.

#### iv. Drug Approval within Health Canada's Biologics and Genetic Therapies Directorate

The approval of biologics, radiopharmaceuticals and genetic therapies is carried out within the Biologics and Genetic Therapies Directorate (BGTD) of HPFB and the process is similar to that for new drugs within TPD, with some differences due to the unique nature of these products. Examples of products regulated by BGTD include cells, tissues and organs (for transplant), vaccines, blood and blood products, gene therapies, and radioactive pharmaceuticals, or radiopharmaceuticals.

Before a biologic can be considered for approval, sufficient scientific evidence must be collected

to show that it is safe, efficacious and of suitable quality, as is the case with other drug submissions. Biologics differ from other drugs for human use, however, in that they must include more detailed chemistry and manufacturing information than is required for other drug submissions. Additional information is required for these products in order to ensure their purity and quality because they are more susceptible than other classes of drugs to contamination and variation from one production batch to the next.

As with other classes of drugs described above, biologics and genetic therapies are granted NOCs and DINs once approved by BGTD. However, marketing of these drugs differs from the other drug categories in that lot batches must be indicated on the packaging. In addition, lots are tested for purity and the frequency of the testing depends on the risk category of the drug.

### C. POST-APPROVAL MONITORING ACTIVITIES – THE FEDERAL ROLE

The safety and efficacy of a drug submitted for approval to Health Canada is largely based on the results obtained from clinical trials conducted on the investigational drug. However, regardless of how well these trials are designed, the safety and effectiveness profile continues to evolve as the drug is used in the general population.<sup>5</sup> This is referred to as the real-world drug safety and effectiveness information. Monitoring of real-world safety and effectiveness is the responsibility of Health Canada which has traditionally been restricted to assessing it with only adverse drug reaction reports. Recently the Drug Safety and Effectiveness Network was created within the Canadian Institutes for Health Research (CIHR) to carry out post-approval studies. CIHR's Strategy for Patient-oriented Research (SPOR) also contributes to post-approval monitoring of drugs by funding investigator-initiated research.

<sup>5</sup> Efficacy is the biologic effect or therapeutic benefit of the drug in a very defined population, effectiveness refers to how well a drug works within the entire population consuming that drug.



## i. Health Canada

Post-approval monitoring activities are the responsibility of the Marketed Health Products Directorate (MHPD) within Health Canada's Health Products and Food Branch (HPFB).<sup>6</sup> MHPD created the MedEffect program in 2005 as part of its strategy to improve safety, effectiveness and access to all regulated therapeutic products, not just pharmaceuticals. The MedEffect website provides a single point of access to: Health Canada's advisories, warnings and recalls; the Canadian Adverse Reaction Newsletter; and the Canada Vigilance Program.<sup>7</sup>

With respect to drugs, the Canada Vigilance Program conducts post-approval safety surveillance by collecting reports of suspected adverse drug reactions (ADRs), analyses them for risk signals and safety trends, and provides risk communications to the healthcare community and the public. Health professionals and consumers can submit online reports of suspected ADRs voluntarily which are then assessed by Health Canada. The program also receives ADRs from drug manufacturers, who are obligated under the Regulations to submit to Health Canada any ADR reports submitted to them. Canada Vigilance includes a publicly accessible and searchable database of all ADR reports called the Canada Vigilance Adverse Reaction Online Database.<sup>8</sup>

## ii. The Canadian Institutes of Health Research

### a. Drug Safety and Effectiveness Network

The Drug Safety and Effectiveness Network (DSEN) within the Canadian Institutes of Health Research (CIHR), was launched in 2009, with the objective of providing evidence to support policy decisions at the federal as well as the provincial level. It is a virtual network of 150 national and international researchers which funds seven research teams in three linked collaborating

centres. A Coordinating Office facilitates network operations and a Steering Committee provides strategic direction and sets research priorities.

DSEN was created to acknowledge the limitation of pre-approval clinical trials and it provides a mechanism by which real world use of approved drugs can be analysed. It responds to requests from drug plan managers, policy-makers, health technology assessors, and regulators to provide additional evidence on the safety and effectiveness of approved drugs.

### b. Strategy for Patient-oriented Research

CIHR's Strategy for Patient-oriented Research (SPOR) supports a continuum of research, from initial studies in humans to comparative effectiveness and outcomes research, and the integration of this research into the health care system and clinical practice. The Strategy funds researcher-initiated studies and aims to translate research findings into cost-effective health care practices with optimal outcomes.



<sup>6</sup> The terms post-market surveillance, pharmacosurveillance and pharmacovigilance are also used in this context.

<sup>7</sup> The MedEffect website is available at: <http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>

<sup>8</sup> The database is available at: <http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php>



## 3. POST-APPROVAL MONITORING OF DRUGS – ISSUES OF CONCERN

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### A. ADVERSE DRUG REACTION REPORTS

Reports of adverse drug reactions (ADRs) have traditionally provided the basis for assessing the post-approval safety and effectiveness of approved drugs in Canada. As described above, Health Canada's Marketed Health Products Directorate (MHPD) is responsible for collecting and assessing ADR reports, as well as responding to safety signals whether through discussions with the relevant pharmaceutical company or risk communications to the public and healthcare community.

In this respect the Regulations provide the following definitions:<sup>9</sup>

“Adverse drug reaction” means a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function;

“Serious adverse drug reaction” means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death; and

“Serious unexpected adverse drug reaction” means a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the label of the drug.

ADR reports submitted to Health Canada originate from both foreign and domestic sources.

Under the Regulations, drug manufacturers are prohibited from selling their products if they fail to meet the requirements for reporting ADRs. Specifically, manufacturers must submit to the Minister of Health, within 15 days, reports of serious ADRs within Canada and as well as foreign reports of serious unexpected ADRs. In addition, manufacturers are obligated to submit annual reports to Health Canada that summarize all ADRs and serious ADRs that the manufacturer has been made aware of and provide a determination of whether the reports affect the risk:benefit profile of their drug. Health Canada has the authority under this provision to request the case reports relating to the annual summary. Finally, Health Canada can request issue-related summary reports from manufacturers for the purpose of assessing safety and effectiveness of a drug at any time.<sup>10</sup> Manufacturers are also required to collect and retain information pertaining to any unusual failure of efficacy of a new drug, although this requirement is not subject to the prohibition of sale as the ones for ADR reporting.<sup>11</sup>

In addition to the ADR reports that Health Canada receives from drug manufacturers, it also obtains voluntarily submitted ADR reports from the public. Health Canada's website provides access to its ADR report form which can be used by consumers as well as healthcare providers to submit information to Health Canada about suspected reactions to pharmaceuticals. The Canada Vigilance program is responsible for collecting and assessing all ADR information. The department also monitors the actions of foreign drug regulators and reviews the scientific literature in order to determine whether there has been a change in a drug's safety or effectiveness that requires further action.

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<sup>9</sup> *Food and Drug Regulations*, C.01.001

<sup>10</sup> *Food and Drug Regulations*, C.01.017-C.01.019.

<sup>11</sup> *Food and Drug Regulations*, C.08.007(h).



In its fall 2011 report, the Office of the Auditor General (OAG) assessed Health Canada's performance in monitoring the safety of approved drugs.<sup>12</sup> The report noted that the department had not adequately fulfilled most of its key post-approval responsibilities. The OAG report stated that in 2010, Health Canada received 330,000 foreign ADR reports but that it did not have the mechanisms in place to receive these reports electronically. It noted that the department did not regularly analyze the reports to detect safety issues and emphasized the importance of assessing foreign reports given the reduced likelihood of rare ADRs occurring in Canada due to the small population, which translates to only 2.6% of the global pharmaceutical market. The OAG report noted that Canada Vigilance received over 30,000 domestic ADRs in 2010 and commented that the department had recently implemented strategies to electronically search domestic ADRs for specific issues such as rare ADRs and ADRs to specific drugs. However, the report also highlighted that while Health Canada had indicated its intention to monitor ADR reports for vulnerable groups, such as children, it had not yet done so.

Many witnesses commented on the low reporting rate for adverse reactions. While there was universal agreement that the ADR reports submitted to Health Canada represented less than 10% of the actual total, most witnesses agreed that it is probably less than 5% and likely closer to 1%. Regardless of the actual reporting rate of ADRs in Canada, the committee heard that the number of ADRs being reported to Health Canada has increased by almost 20% in the past five years. Health Canada reported that in 2010-2011 it had received 33,000 domestic ADRs; 82% of these are submitted by industry and the remainder from consumers and the healthcare community. With respect to the original source for the ADR reports, Health Canada specified that consumers submit 27%, physicians submit 24%, nurses submit 17%,

pharmacists submit 13%, and the remaining ADR reports are submitted by healthcare professionals not otherwise specified.

Witnesses spoke of the difficulty of submitting ADR reports to Health Canada and of the frustration over the lack of feedback from the department following a report submission. Health professionals indicated that the time required to prepare and to submit an ADR report is a disincentive to offer such information to the regulator. The failure of Health Canada to acknowledge an ADR report submission, or to follow-up on it, serve as further disincentives for the public to provide ADR information. Anna Reid, President of the Canadian Medical Association and Barbara Mildon, President of the Canadian Nurses Association, commented on the need for user-friendly, easily accessible ADR forms that can be submitted electronically. The committee heard that linking Health Canada's ADR report form through the electronic health record and the electronic medical record would facilitate reporting for health professionals and would increase the quantity and quality of ADR reports for Health Canada. It was also suggested that such a format might facilitate implementing a feedback mechanism whereby the department could acknowledge and follow-up on ADR reports.

The committee was told of initiatives in the U.S. and the United Kingdom that serve to draw attention to the possibility of ADRs and encourage reporting. In the U.S., certain drugs with known serious risks must include a 'black box' warning on the label and patients must be supplied with information when these drugs are dispensed to them. This was compared to Health Canada's practice of issuing safety information letters. In the United Kingdom, new drugs must carry a 'black triangle' warning for three years following market approval. This reflects the observation that adverse reactions cannot be completely defined following

<sup>12</sup> Office of the Auditor General, Chapter 4, "Regulating Pharmaceutical Drugs – Health Canada," 2011 *Fall Report of the Auditor General of Canada*.





clinical trials, and that a significant proportion of new drugs are found to be associated with serious adverse reactions. Both of these warnings alert the prescriber, the dispenser and the consumer to the increased potential for ADRs and can consequently increase the likelihood of reporting those ADRs. The committee was told about an initiative piloted in Boston, Massachusetts, aimed at improving ADR reporting which involved an automated phone system that called patients four weeks after being prescribed a new medicine and enquired about adverse events. Potential drug-related incidents would then be followed up individually by health professionals. In fact, the committee notes a similar initiative by Canadian researchers and encourages further adoption of this practice should it be shown to be as effective as early results suggest.<sup>13</sup>

## B. DETECTION OF SAFETY ISSUES

ADR reports received by the Canada Vigilance Program, along with other sources of ADR information, are assessed to determine whether there is an identifiable safety issue, or 'signal', that requires further action. Health Canada described the challenge in assessing ADR information to determine whether adverse reactions are linked to a specific drug and not due to other variables such as the health condition for which the drug has been prescribed, a co-existing health condition, or another food or drug consumed by the individual.

Once detected, Health Canada indicated that it applies a risk-based approach which prioritizes safety issues and analyzes them to determine if further action is warranted and necessary. This approach results in a priority rating of high, medium or low. High priority safety issues relate to adverse reactions that are unknown or unlabeled and will likely require action; medium priority issues would include less serious adverse reactions that are likely to require labelling changes; and low priority issues could relate to known and labeled

adverse reactions that are unlikely to result in action by the department.

Health Canada has implemented performance standards in this regard whereby it aims to complete assessments of high-priority safety issues within 80 working days, medium-priority issues within 130 working days and low-priority issues within 200 working days. However, the OAG testified that its 2011 audit found Health Canada to have been slow to respond to potential safety issues. The report revealed that, in 2009 and 2010, the department took at least one year to complete over half of the 54 assessments which required labelling changes, all of which were categorized as medium- or low-priority. The OAG found that the performance targets were not being met a significant portion of the time. The committee was told by the department that the OAG audit was conducted prior to the implementation of updated cost-recovery fees. The department emphasized that this has resulted in greater revenue as well as long-term stable funding to carry out its regulatory functions including safety assessments of post-approval drugs. As a result, Health Canada noted that, in 2011, it had identified 50 signals and completed 91% of signal assessments within its performance targets.



<sup>13</sup> A. Forster and C. Auger, "Using Information Technology to Improve the Monitoring of Outpatient Prescribing," *Journal of the American Medical Association Internal Medicine*, February 4, 2013, doi:10.1001/jamainternmed.2013.2002.



Some witnesses voiced concern about the manner by which Health Canada determines whether or not a signal has been detected. They suggested that this process should be more transparent. In addition, the committee was told that the department should be more transparent about the drugs it is assessing. Health Canada noted that on occasion it may issue warnings or other public advisories on potential safety risks before completing a safety assessment.

### C. ELECTRONIC RECORDS

Throughout this study, the reporting of ADRs was frequently linked to electronic medical and health records. The electronic medical record (EMR) stores a patient's complete health information (such as lab results, doctor's notes, medical history, etc.) in a single location, such as a physician's office or a community health centre. The electronic health record (EHR) is a secure and private record that provides collective lifetime health information about an individual that comes from various sources such as physicians, hospitals, diagnostic laboratories and pharmacists. The EHR can be accessed by only authorized health professionals.

The committee was told that implementation of EMRs and EHRs across Canada is progressing as planned. With respect to EHRs, the target of having 50% of Canadians covered by 2010 was only missed by three months. The target for 100% coverage was originally set for 2016 and Canada Health Infoway indicated that they expect this target to be met. The committee also heard that 60-65% of Canadians will have EMRs at their points of care and that these will be connected through their EHRs by the end of 2014. Compatibility and linkability of EMRs with the EHR was mentioned as one of the limiting factors in progressing to 100% coverage across Canada.

Several witnesses were supportive of the implementation of EMRs and EHRs and suggested that these could play a significant role in ADR reporting and by extension facilitate Health

Canada's responsibility to identify potential safety issues. Health professionals voiced strong support for incorporating ADR reporting into the EMR. They commented on the time required currently for submitting ADR reports and suggested that such an advance would significantly simplify the process and would encourage them to undertake ADR reporting more frequently. The committee heard that there is considerable collaboration amongst all stakeholders to create a compatible and linkable system for all Canadians.

Sylvia Hyland, Vice-President of the Institute for Safe Medication Practices, revealed that 40 organizations across Canada have collaborated on the Canadian Pharmaceutical Bar Coding Project. This initiative was described as one mechanism by which medication safety could be enhanced. The standardized automated pharmaceutical identification system could be linked through the EHR to improve the capacity to capture data on the use of any specific medicine.

Health Canada indicated that it is studying the potential of EMRs and EHRs as part of a strategy to increase the quantity and quality of ADR reports. However, as noted in the OAG report and confirmed by several witnesses during the course of this study, including Health Canada officials, the department does not yet have full capacity for electronic submission of ADRs. While it has very recently begun to allow a limited number of manufacturers to submit ADR reports electronically, the capability will not fully extend to all manufacturers and the public until the end of 2014.

### D. RISK COMMUNICATIONS

Once a safety issue has been identified, the Canada Vigilance program is responsible for alerting Canadians by issuing risk communications. The committee heard that risk communications used by Health Canada are designed to target specific groups. For example some communications may be highly technical and aimed only at a sub-group



of healthcare providers, while others will be aimed at the broad public with messaging relevant to the risk involved. Such communications can include public advisories and warnings on the Health Canada website or in the media, ‘Dear Doctor’ letters, and updates to the MedEffect Newsletter. Health Canada indicated that it had issued 154 risk communications in 2011.

The committee was told that in some instances Health Canada relies on the drug manufacturer to issue risk communications to all physicians. It also heard that risk communications can be delayed until necessary label changes are implemented, and that sometimes such changes involve multiple drugs. However, departmental officials emphasized that they do not delay the issuance of urgent risk communications.

Several witnesses expressed concerns about the effectiveness of Health Canada’s risk communications strategy. Robyn Tamblyn, Scientific Director in the Department of Epidemiology, Biostatistics and Occupational Health at McGill University, pointed out that most countries struggle to achieve an effective mechanism by which to get information out to health providers and the public. While it was noted that the number of such communications had been increasing lately, the committee also heard that health professionals often don’t have the time to thoroughly review all of the material. The OAG pointed out that there have been no target timelines established for the issuance of risk communications. It indicated that for half of the risk communications evaluated by the OAG, the department had taken over two years to complete the entire process of assessing a potential safety issue, updating the drug’s label and then issuing the risk communication. Finally, the OAG noted that Health Canada had progressed little on its commitment to assess the effectiveness of the risk communication strategy.

## E. DRUG INFORMATION FOR PATIENTS AND HEALTH PROFESSIONALS

Health Canada includes a drug’s product monograph as part of its label.<sup>14</sup> The product monograph is a lengthy and technical document that is publicly available on the department’s website for most approved prescription drugs.<sup>15</sup> It includes information about the properties, claims, indications, and conditions of use for the drug, and any other information that may be required for its optimal, safe, and effective use. Health Canada’s guidance to the pharmaceutical industry on the preparation of the product monograph states that:

“A product monograph should include appropriate information respecting the name of the drug, its therapeutic or pharmacologic classification, its actions and/or clinical pharmacology, and its indications and clinical uses. The monograph should also include contraindications, warnings, precautions, adverse reactions, drug interactions and effects on laboratory tests, symptoms and treatment of overdose, dosage and administration, storage and stability, pharmaceutical information, dosage forms, pharmacology, toxicology, microbiology, special handling instructions, information on clinical trials, information for the consumer, references, and the dates of the initial printing and current revision.”<sup>16</sup>



<sup>14</sup> The *Food and Drugs Act* defines ‘label’ as any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic device or package (section 2). This definition is much broader than what consumers might assume to be the label, that is, simply that which is affixed to the product’s container. This concept of label is defined as ‘inner label’ under the *Food and Drug Regulations* (A.01.010).

<sup>15</sup> Prescription drugs with lengthy market histories and established safety profiles may not have product monographs.

<sup>16</sup> Health Canada, “Guidance for Industry: Product Monograph”, 2003, page 1.



This document is prepared in draft form to accompany a manufacturer's drug submission and is modified as necessary to accompany the NOC issued by Health Canada. The product monograph includes three parts: health professional information; scientific information; and, consumer or patient information.

Part I is product information for health professionals who prescribe and dispense a drug, as well as for those who care for the patients who consume a drug. The committee did not hear any supportive testimony with respect to this section of the product monograph and its usefulness to health professionals. On the contrary, it heard that physicians are most likely to get their information about drugs, particularly new medicines, directly from drug company representatives.

Part III must be written in lay-terms, understandable to the general public and cannot be promotional. It provides information about the drug, what it is and what it does, as well as specifies when it should not be used. Precautions, food, drug and beverage interactions, and warnings are also provided. Warnings of serious public health concerns must be presented as boxed information. The consumer information section of the product label also provides information about proper use of the drug including dosage, known side-effects and storage and indicates how to report adverse reactions.



Patient advocates expressed concern about the information that is available to consumers, particularly that there is too much industry input into what is made available. The committee heard that few patients are aware that Part III of a product's monograph is intended as consumer information, or that it is available to them via the Health Canada website. Witnesses suggested that consumers rely on the information given to them by pharmacists but heard that the information supplied at the point of sale is not subject to Health Canada oversight. While pharmacies may prepare patient information documents from the product's label, which has been approved by Health Canada, they may also derive them directly from information supplied by the manufacturer. The committee was told that this information may not provide a complete overview of the potential risks associated with a drug. Terence Young, founder of Drug Safety Canada and a Member of Parliament, urged the creation of Patient Information Leaflets (PILs), prepared by the regulator. PILs would be standardized, plainly-worded and concise brochures that accompany the drug when it is dispensed.

## F. POST-APPROVAL STUDIES

The committee was told that prescription drugs are linked to the cause of death 20-25% of the time, and that in the majority of these cases, the death was preventable. Witnesses spoke of the higher prevalence of safety issues with fast-tracked drugs. While this is not a term that Health Canada uses, it is assumed to include both the priority review and NOC/c product submission processes. Only the NOC/c process has a reduced threshold of evidence for clinical safety and efficacy and as described earlier, includes a requirement for the manufacturer to carry out post-approval studies in order to bring the evidence-base up to the standard for other NDSs.

In addition to the need for post-approval studies for drugs granted a NOC/c, several witnesses emphasized the need to conduct post-approval studies on other drugs for a variety of reasons. It



was generally agreed that real-world safety and effectiveness can only be measured accurately in post-approval studies and that the ADR reports collected by Health Canada cannot provide the same level of comprehensive review. All stakeholders acknowledge that the information collected during clinical trials is limited and cannot be expected to reflect real-world use regardless of how well the trials were designed and carried out. In some instances, ADRs may have been noted during clinical trials and should be monitored when the drug is approved for the general public. In other instances, ADRs may be too rare to have been picked up in clinical trials and will only be identified in post-approval monitoring.

The committee was told that post-approval studies should also be conducted in order to better define the effectiveness of a drug. Comparative effectiveness studies, whereby a new drug's effectiveness is compared to that of an existing drug, are not always conducted during the clinical trial phase. This information is critical not only to drug insurers but also to prescribers who need to know which drugs they should consider as the first line of therapy and which should be considered as secondary. Drug effectiveness studies are also useful in determining which sub-groups of the population respond well to a drug and which are most vulnerable to adverse reactions.

Several witnesses highlighted the role of post-approval studies in realizing the potential of personalized medicine, or pharmacogenomics. Pharmacogenomics is the study of variations of genetic characteristics as related to drug response. The committee was told about post-approval studies that have been able to define populations that are at risk for adverse reactions to certain drugs and other sub-groups for whom certain drugs will have little or no effect.

In regard to post-approval studies, the committee was told that CIHR's SPOR supports comparative effectiveness research and that the Collaborative

Centre for Prospective Studies within CIHR's DSEN includes a personalized medicine component to promote pharmacogenomics research, an active surveillance component and a comparative effectiveness component. The committee also heard about the Canadian Pharmacogenomics Network for Drug Safety, which is an initiative that aims to optimize treatment for patients while saving costs to the health system.

However, CIHR is not tasked with a comprehensive drug monitoring responsibility. CIHR funds researcher-initiated studies under SPOR while DSEN responds to queries from Health Canada as the regulator, all federal/provincial/territorial drug plan managers, as well as organizations mandated to support decision-making by those bodies. DSEN does not fund investigator-initiated research nor does it respond to queries from voluntary health organizations, for-profit enterprises, individual practitioners, community pharmacies or the public. The committee was told that DSEN hopes to extend the list of organizations and individuals who are eligible to submit queries to DSEN, but that it is operating at full capacity at this time.

In addition to DSEN's capacity to carry out post-approval studies on drug safety and effectiveness, some witnesses commented on the organization's structure and governance. Robert Peterson, Executive Director of DSEN, indicated that results of its studies are 'conveyed' to Health Canada but the committee learned that it has no regulatory responsibility or authority. In other words, there are no regulatory requirements for DSEN to fulfill its mandate, nor parameters on how it should be fulfilled, and DSEN has no authority to act on the information that it acquires through these studies or the ability to ensure that its findings are acted upon. In addition, the committee learned that although DSEN was created with initial funding until 2015, it has not been created by legislation and therefore there is no assurance that it will continue to exist or that funding will be adequate.



At the present time Health Canada has no authority to require that post-approval studies be conducted. Therefore, post-approval studies, which are not enforceable, are limited to: drugs for which a NOC/c has been issued and for which the manufacturer has been tasked with carrying out the studies; drugs for which the manufacturer has re-assessed its safety and effectiveness due to a change in the information it has collected and is required by regulation to supply to Health Canada; and, studies in response to queries from a defined list of entities. The first two categories rely on the drug industry to carry out studies which may result in a less favorable risk/benefit profile, which is a disincentive to carry out the research. The third category relies on a problem first being identified and on DSEN having sufficient resources to respond to the query in a timely way.

As mentioned above several witnesses commented on the need to monitor the safety and effectiveness of approved drugs within various sub-groups of the population. Health Canada agreed that it is essential to continue to follow drugs post-approval in order to determine their safety and effectiveness within different population groups such as children, pregnant and nursing women or the elderly. They emphasized the importance of ensuring that ADR reports contain the required information in order to separate out sub-groups within the population as well as ensuring that their database permits them to separate out these groups. Departmental officials also noted that they can request that a



drug's manufacturer carry out post-approval studies within sub-population groups. They indicated that some manufacturers have expressed limited willingness to carry out certain types of studies.

Several witnesses discussed the need for more post-approval monitoring of drugs within various sub-groups. With respect to the pediatric population, despite Health Canada's indication that a systematic approach is already in place to monitor this group, the committee was told that more needs to be done. Legislation has been in place for many years in the U.S. that authorizes the Food and Drug Administration (FDA) to require a company to carry out studies in the pediatric population for adult conditions that also exist in children. In terms of pregnant and nursing women, the committee heard that this information is not always noted in ADR reports, making signal detection difficult. Witnesses spoke of the need to actively pursue post-approval studies in all population groups relevant to the drug in question.

The committee is concerned that Health Canada has not demonstrated a capacity to detect safety issues within sub-groups of the population in order to submit queries to DSEN for follow-up studies. It is also concerned that manufacturers will not conduct the necessary post-approval studies and that Health Canada has no authority to require manufacturers to do so.

## G. RESOURCES DEDICATED TO POST-APPROVAL MONITORING ACTIVITIES

Several witnesses commented on the lack of resources being dedicated to post-approval monitoring activities and urged greater funding for MHPD as well as DSEN. The committee heard that MHPD receives only about half the funding that TPD does but that pre-and post-approval activities should be equally resourced. Officials from the U.S. FDA described the 2007 legislative changes to their post-approval monitoring activities, which included



an obligation to place equal emphasis on pre- and post-approval activities

## H. TRANSPARENCY AND INDUSTRY INFLUENCE

A persistent theme throughout this phase of the study was the lack of transparency at Health Canada. Linked to this issue, according to several stakeholders, is a claim of perceived influence of the pharmaceutical industry on the actions of the department. The OAG noted in the 2011 report that the department has taken steps to increase their transparency such as making publicly available the Summary Basis of Decision documents for drugs that receive approval. However, the report also noted that the department needed to improve transparency of approvals with conditions, rejections and withdrawals of drug submissions. Health Canada responded that public access to information about decisions for these categories of submissions would begin in September 2012, with publication of a notice in June 2012 to advise stakeholders. At the time of this report, it was unclear to the committee whether public access had been expanded to include the broader range of both positive and negative decisions.

Some witnesses commented that Health Canada should make public the names of drugs for which the department has identified a potential safety issue and is investigating further. It was suggested that the department should be more transparent regarding ongoing discussions with companies when labelling and safety issues are being discussed. They pointed to the prolonged timelines, which the OAG notes in its report, of Health Canada taking years to achieve labelling changes and issuing risk communications. With respect to the work of DSEN, the pharmaceutical industry stated that it felt it was entitled to know when one of its products becomes the focus of such an investigation. In this regard, the committee was told of the Observational Medical Outcomes Partnership in the U.S. and the

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium initiative in the European Union. These initiatives include the industry along with drug regulators and academia in the evaluation of possible links between a drug and a health-related condition. However, most witnesses supported DSEN's policy not to inform manufacturers of ongoing studies and urged that the drug industry have as little influence in this regard as possible.

Finally, the committee heard concerns regarding industry's role in conducting some post-approval studies and in preparing some of the documents that Health Canada uses when exercising its post-approval monitoring activities, such as the product monograph, discussed above, and risk management plans (RMPs), which the department can request from drug manufacturers which outline actions that can be taken to prevent or mitigate risks associated with a particular drug.





## 4. IMPROVING POST-APPROVAL MONITORING OF DRUGS – IMPLEMENTATION OF EFFECTIVE ACTIVE SURVEILLANCE PRACTICES

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### A. MODERNIZE THE LEGISLATIVE AND REGULATORY FRAMEWORK FOR DRUGS

Historically, Health Canada's approach to post-approval drug monitoring has been to rely on the ADR reports that it receives from drug manufacturers and the public to assess risk and determine the need for further investigation. It has also often reacted to the actions of other federal regulators, particularly the FDA, to take action itself. However, Health Canada has been taking steps in recent years to adopt a more active approach to drug surveillance in favour of an active one. This approach is referred to by the regulator as a life-cycle approach to drug regulation.

The intent to advance to this model from the traditional point-in-time regulation was presented in Health Canada's *Blueprint for Renewal II: Modernizing Canada's Regulatory System for Health Products and Food* and in the Government of Canada's *Food and Consumer Safety Action Plan*, both on 2007. Since that time Health Canada has repeated its commitment to adopting a life-cycle approach to drug regulation. It has consulted broadly on the subject, has established the DSEN, and has begun to request documentation from the drug industry that is consistent with similar approaches in other jurisdictions.

A critical element however, to progressing to the life-cycle approach, is legislative and regulatory modernization. An attempt was made in this regard in 2008, when Bill C-51, An Act to amend

the *Food and Drugs Act*, was tabled in the House of Commons. This bill proposed several new authorities for the Minister of Health consistent with the life-cycle approach including the authority to: require post-approval studies; require label changes; require the re-assessment of a drug's safety and effectiveness; and, publicly disclose information about the risks and benefits of a drug. In addition, the bill included a recall provision. The Minister of Health does not currently have the authority to issue a mandatory recall under the *Food and Drugs Act*. The bill also proposed to include provisions regarding the issuance of market authorizations for drugs, including all of the related authorities pertaining to suspensions, cancellations, etc. Currently, the Act does not address drug approval or any of the requirements in order that a drug may be sold in Canada. Bill C-51 died on the Order Paper at the dissolution of the 39<sup>th</sup> Parliament in September 2008 and no bill containing similar provisions has been introduced since that time.

The committee heard overwhelming testimony in support of the life-cycle approach and the need for new legislative authorities in order to properly implement it. For example, Ingrid Sketris from the Health Council of Canada, referenced its report entitled *Keeping an Eye on Prescription Drugs, Keeping Canadians Safe*. The report commends Health Canada's two initiatives to implement active surveillance, the creation of DSEN and the proposed life-cycle approach to drug regulation, but notes that greater legislative authority is required to implement the new regulatory framework.<sup>17</sup> While the committee is encouraged

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<sup>17</sup> Health Council of Canada, "Keeping an Eye on Prescription Drugs, Keeping Canadians Safe – Active Monitoring Systems for Drug Safety and Effectiveness in Canada and Internationally," November 2010.





that the pharmaceutical industry voiced support for Health Canada's recent initiative to request risk management plans and periodic safety update reports from drug manufacturers, it notes that the department does not have the authority to compel them to provide such documents. The committee agrees with Carole Bouchard, Executive Director of the National Association of Pharmacy Regulatory Authorities, who stated that implementing the necessary legislative authorities in order to fully operationalize a life-cycle approach to post-approval monitoring of drugs, should be a priority of the federal government.

Witnesses suggested that Canada has not kept pace with its global partners in this regard. The European Union and the United States have modernized their approaches to drug regulation in recent years, including new legislative authorities. Pharmacovigilance practices in the European Union were most recently updated under a 2010 Directive which requires RMPs for new products, simplifies ADR reporting, sets out clear roles and responsibilities for signal detection, improves transparency and risk communications, etc.<sup>18</sup>

Officials from the FDA described the updated U.S. approach to the committee, which has been implemented pursuant to their *Food and Drug Administration Amendments Act* of 2007 (FDAAA). The FDAAA also introduced mandatory registration of a broad set of data for clinical trials, as indicated in this committee's report on clinical trials tabled on November 1, 2012. The FDAAA was a comprehensive piece of legislation that amended and re-authorized various statutes. It granted new authorities, responsibilities and resources to the FDA to enhance post-approval activities and contains new authorities to require: post-market studies; labeling changes; and, Risk Evaluation and Mitigation Strategies (REMS). Further, it requires that the FDA carry out increased activities for active post-market risk identification and analysis.

In particular, it provides for the tools and methods to enable and facilitate data access and analysis. Officials described the changes within the FDA as a result of the FDAAA which have brought about a new approach to monitoring drug safety. The resources granted under the FDAAA have resulted in equal emphasis on pre- and post-market activities. Officials described the new authorities as useful, and that they can only be used when specified conditions have been met. They emphasized that, like Health Canada, the preferred approach is to work cooperatively with the industry although they suggested that it is helpful to "have a hammer at the end of your hand on some matters."<sup>19</sup>

Health Canada officials clearly expressed the department's intention of adopting a comprehensive life-cycle approach to regulating drugs. They indicated that while the authority to require drug companies to undertake certain actions, such as label changes, post-approval studies and drug recalls, would be consistent with a life-cycle regulatory framework, the preferred approach would remain persuasion. While the committee agrees that such authorities should be used prudently, it would like to point out that the department has no ability to invoke penalties for non-compliance unless the company has failed to comply with a legislative or regulatory requirement.

The committee did not undertake a thorough study of all the provisions in Bill C-51 that applied to the management of pharmaceuticals, but notes that there was considerable support for the proposed bill among the witnesses who testified. However, given Health Canada's continued commitment to implement a life-cycle approach to drug regulation and the pattern of legislative change that has been noted in other jurisdictions, the committee is convinced that new authorities must be introduced under the *Food and Drugs Act*.

<sup>18</sup> Health Canada, HPFB International Pharmacovigilance Symposium, June 6, 2012, [http://www.jptcp.com/files/HPFB\\_International\\_Symposium\\_June\\_6.pdf](http://www.jptcp.com/files/HPFB_International_Symposium_June_6.pdf)

<sup>19</sup> Dr. Robert Temple, Deputy Center Director for Clinical Science, U.S. FDA, Evidence, October 31, 2012, [http://www.parl.gc.ca/Content/SEN/Committee/411/soci/24ev-49770-e.htm?Language=E&Parl=41&Ses=1&comm\\_id=47](http://www.parl.gc.ca/Content/SEN/Committee/411/soci/24ev-49770-e.htm?Language=E&Parl=41&Ses=1&comm_id=47)



The committee therefore recommends that the Government of Canada introduce legislation which includes authorities for drug management. These authorities should include, but not be limited to:

- The authority to require post-approval studies;
- The authority to require label changes;
- The authority to require re-assessment of a drug's safety and effectiveness;
- The authority to disclose publicly information about a drug's risks or benefits;
- The authority to require Risk Management Plans and Periodic Safety Update Reports; and
- The authority to issue mandatory drug recalls. [recommendation 1]

The committee acknowledges that legislative changes alone are not sufficient to implement a comprehensive life-cycle approach to drug regulation. In this regard, it notes that Health Canada has conducted consultations on the issue of modernizing the regulatory framework for drugs. Recently the department made publicly available on its website a summary of technical discussions that it held in late 2010 and early 2011 on all aspects of drug management but with an emphasis on post-approval activities. However, the department has indicated its intention to pursue active surveillance of pharmaceuticals by applying a life-cycle approach to drug regulation for almost ten years. The department stated some time ago that the drug regulatory framework was outdated, limited and inflexible.<sup>20</sup>

The committee therefore recommends that the Minister of Health ensure publication of a modernized regulatory framework for drugs that applies a life-cycle approach to drug management in the *Canada Gazette*, beginning in 2013. [recommendation 2]

The committee further recommends that long-term studies of drug safety must be included as part of a life-cycle approach to drug management. [recommendation 3]

The committee learned throughout the course of this study that there has been a trend internationally to dedicate more resources to the post-approval phase of drug regulation. In fact, Health Canada noted that it is not adequately resourced to ensure long-term sustainability and efficiency of post-approval activities.<sup>21</sup> This must be in addition to the resources for pre-approval regulation, not at the expense of it. Funding for MHPD has increased relative to that of TPD and BGTD between 2004 and 2010. The committee would like to see this trend continue with the goal of reaching equal funding for pre and post-approval drug regulatory activities.

The committee therefore recommends that the Minister of Health work to achieve equal funding for both pre- and post-approval drug regulatory activities and ensure that post-approval resources are adequate for implementation of a comprehensive life-cycle approach to drug management. [recommendation 4]

<sup>20</sup> Health Canada, "Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food," October 2006, <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/blueprint-plan-eng.php>

<sup>21</sup> Ibid., page 7.



## B. ENSURE INDEPENDENCE AND EFFECTIVENESS FROM THE DRUG SAFETY AND EFFECTIVENESS NETWORK

Despite broad support among witnesses for Health Canada to have the authority to require drug manufacturers to carry out post-approval studies, there was also general agreement that such studies should not be conducted exclusively by the pharmaceutical industry. Mary Wiktorowicz, Professor at the School of Health Policy & Management at York University, emphasized that active surveillance should be at arm's length of the pharmaceutical industry. In addition, the committee was told that companies often do not want to conduct such studies and that it can be difficult to get them to do so. However, some witnesses suggested that drug companies may be suited to conducting long-term follow-up studies for some drugs since they maintain patient registries.

Overall the committee heard strong support for DSEN and applauded its creation as an important step towards a life-cycle approach to drug regulation. The integrity of the DSEN structure or of the researchers working within it was not questioned. Similarly, the list of those eligible to submit queries to DSEN was essentially viewed by the committee as reasonable, especially at this early stage of DSEN's development. It strongly encourages DSEN to continue to evaluate its resources and capacity with a view to modifying the list of those who may submit queries whenever possible.

Being within CIHR, DSEN benefits from the reputation that CIHR has as a highly regarded agency responsible for ensuring the highest standards of scientific excellence in health research. CIHR is also well positioned to take advantage of the research capacity available amongst clinicians to create the networks best suited to responding to post-approval drug queries. However, the committee notes the reservations voiced by one

witness that CIHR's mandate is to fund research, not to supplement the work of the federal regulator or respond to queries. In addition, the committee understands the reservations expressed by several witnesses about DSEN's independence. Some suggested that DSEN is not far enough removed from industry's influence, since DSEN's grants and awards are administered through CIHR which has industry representation on its governing board. Trudo Lemmens, Scholl Chair in Health Law and Policy at the University of Toronto, suggested that CIHR is promoting closer collaboration with the pharmaceutical industry. The committee heard that CIHR needs to either re-consider its relationship with industry or create more structural independence from it, or DSEN needs to be more independent from CIHR. However, given that CIHR is currently viewed by Canadians as a trustworthy and well-regarded organization, and that DSEN is in its early phase of development and has the support of many stakeholders, the committee is not prepared to recommend any structural changes at this time.

In addition to independence, the committee is concerned about two other aspects of DSEN's work. First, it is concerned that there is no formal mechanism to ensure that DSEN findings are translated into action, for example that label changes found necessary as a result of such studies are implemented by Health Canada. The committee agrees with those witnesses who proposed that this link be established in order to increase transparency of the post-approval studies being undertaken, and to provide accountability for the resources being dedicated to DSEN as well as of Health Canada and its responsibility to implement the findings of DSEN should they impact on a drug's safety and effectiveness profile. It supports the suggestion that this may be accomplished in a manner similar to that established under the FDAAA. Second, the committee is concerned that DSEN has not been created as a permanent entity



within CIHR. It was told that there is no obligation to maintain funding, or even to guarantee the on-going existence of DSEN.

The committee therefore recommends that the Minister of Health order a comprehensive and independent assessment of the work of the Drug Safety and Effectiveness Network (DSEN) and that a report be submitted to the President of the Canadian Institutes of Health Research (CIHR) as well as to the Minister of Health and be made publicly available. The report should provide:

- An analysis of DSEN's ability to operate independently from both CIHR and Health Canada;
- A recommendation of DSEN's budgetary needs in order to conduct the necessary post-approval studies;
- A discussion of the findings that DSEN has conveyed to Health Canada and how these have been acted upon by the regulator;
- A comparison of DSEN's performance relative to other international post-approval drug research networks; and
- Advice on whether DSEN should be re-structured in order to best fulfill its mandate. [recommendation 5]

The committee further recommends that the Minister of Health provide assurance that the Drug Safety and Effectiveness Network is:

- a permanent entity with on-going and sustained funding; and
- responsible for its own budget.

[recommendation 6]

The committee further recommends that the Minister of Health establish an oversight mechanism to regularly review the findings of the Drug Safety and Effectiveness Network and make this information publicly available. [recommendation 7]

### C. OPTIMIZE THE RESEARCH MODEL WITHIN THE DRUG SAFETY AND EFFECTIVENESS NETWORK

The committee is supportive of the research model adopted by DSEN. It currently funds seven research teams in three collaborating centres, encompassing over 150 researchers. The three centres are: the Collaborating Centre for Observational Studies; the Collaborating Centre for Prospective Studies; and the Collaborating Centre for Network Meta-Analysis. The seven research teams housed within these three centres employ six different research methodologies that allow DSEN to help fill knowledge gaps regarding drug safety and effectiveness. Randomized clinical trials are not one of the methodologies used by DSEN, although it suggested that this may become part of its research model in the future. In this regard, the committee heard that some categories of post-approval monitoring should be conducted as clinical trials.



The committee commends DSEN on the inclusion of clinicians within its research model and agrees that it is important to include those who prescribe the drugs and who see their effects, and to encourage them to become involved in active surveillance of drug safety and effectiveness. Including clinicians who have an interest in monitoring drug safety addresses the frustration expressed that there is no feedback from Health Canada when physicians report ADRs. Janet Currie of the Psychiatric Medication Awareness Group suggested that by including them within the active surveillance model the quality of information obtained will increase.

The committee was told of the Canadian Pharmacogenomics Network for Drug Safety which links pediatric hospitals across Canada, including the clinics affiliated with those hospitals, and encourages the clinicians to become involved in active surveillance of the drugs that they prescribe. As described by Bruce Carleton, a Professor in the Department of Pediatrics at the University of British Columbia, the model requires recruiting and training individuals at each healthcare site to be responsible for thoroughly assessing safety and effectiveness issues and to submit comprehensive ADR reports. This approach changes the focus from spontaneous and sporadic ADR reporting without quality control to concentrated ADR reporting by trained individuals so that quality is assured. This model was described as being transferable to a broader range of healthcare settings and has shown itself to be effective in defining genomic markers that can affect both a drug's safety and effectiveness. In this way, the model successfully advances pharmacogenomics, or personalized medicine, one of DSEN's stated priorities.

In this regard, the committee would like to emphasize its Clinical Trials Report and the recommendation to promote the creation of research networks.<sup>22</sup> As such, the committee suggests that the new clinical trial infrastructure may add to the

research capacity available to DSEN which it should incorporate into its current and future activities.

**The committee therefore recommends that the Drug Safety and Effectiveness Network:**

- incorporate the model used by the Canadian Pharmacogenomics Network for Drug Safety as a means to apply active post-approval surveillance to adverse drug reaction reporting and,
- make use of the research network capacity proposed in the committee's clinical trials report of November 2012. [recommendation 8]

#### D. IMPROVE DATA COLLECTION THROUGH ELECTRONIC HEALTH RECORDS

In order for DSEN and Health Canada to successfully accomplish their responsibilities in post-approval monitoring, they must have access to the best possible data. Regardless of the quantity and quality of ADRs submitted to Health Canada, accurate assessment of risk requires information about the number of prescriptions filled for any particular drug. DSEN's work also requires access to multiple sources of patient data in order to conduct their analyses. Currently it assesses public and private administrative health data to conduct its analyses. The committee agrees with those witnesses who suggested that, although the data available through these sources is extensive, it is also variable in terms of content.

With respect to capturing data on dispensed drugs, which can be useful to both Health Canada and DSEN, the committee was told by Jennifer Zelmer, Senior Vice-President of Clinical Adoption and

<sup>22</sup> Recommendation 5 of the Clinical Trials Report recommended that the proposed National Coordinating Office for Clinical Trials encourage the creation of research networks.



Innovation at Canada Health Infoway, that drug information systems have been put in place in all of Western Canada. In particular, British Columbia's PharmaNet program compiles data on all prescription drug sales in the province, regardless of whether the prescription is paid for through a public or private drug plan, or paid for by the consumer. The committee applauds this effort and suggests that this model may present an opportunity to capture prescription drug use data across the country by urging all jurisdictions to adopt a similar model. The resulting databases of dispensed prescription drug data should be compatible to and linkable with patient EHRs, which will also link to ADR information. The committee would also like to re-iterate the recommendations it made in its report entitled *Time for Transformative Change: A Review of the 2004 Health Accord*, urging investment, development and uptake of EMRs and EHRs.

**The committee therefore recommends that the Minister of Health meet with provincial and territorial counterparts to discuss implementation of a system similar to British Columbia's PharmaNet in all jurisdictions in order to capture data on all prescription drugs dispensed.** [recommendation 9]

**The committee further recommends that the Minister of Health urge provincial and territorial counterparts, through the work of Canada Health Infoway, that the national system of electronic health records must be linkable to and compatible with the electronic system that captures data on dispensed prescription drugs.** [recommendation 10]

## E. FACILITATE ADVERSE DRUG REACTION REPORTING

Several witnesses discussed the current ADR reporting requirements. While the committee is concerned about the number of ADRs that are reported to Health Canada, it agrees with all witnesses who supported voluntary reporting and it does not support mandatory ADR reporting for health professionals. It agrees that this approach would not be enforceable and would likely not result in greater reporting in any case. Reporting for drug manufacturers should remain mandatory.

In order to encourage voluntary ADR reporting among health professionals, it must be easier to do than was described to the committee. Health Canada must ensure that all ADR reports can be submitted electronically and for those that are submitted by fax, mail or phone, Health Canada must be able to add them to the electronic database as quickly as possible. With respect to facilitating access to Health Canada's online ADR report form, the committee agrees with witnesses who urged that it be incorporated into electronic medical records and electronic health records.

**The committee therefore recommends that the Minister of Health ensure that Health Canada is represented at ongoing federal/provincial/territorial discussions regarding the implementation of electronic medical records and electronic health records to promote the inclusion of the adverse drug reaction reporting form.** [recommendation 11]



## F. IMPLEMENT POST-APPROVAL STRATEGIES FOR POPULATION SUB-GROUPS

Several concerns were raised pertaining to monitoring the safety and effectiveness of approved drugs within sub-groups of the population.

Françoise Baylis, Canada Research Chair within the Faculty of Medicine at Dalhousie University, emphasized that post-market monitoring activities should be designed to identify safety and effectiveness issues among sub-groups, including gender-based differences. In fact, the OAG report noted that Health Canada had not implemented a strategy for monitoring ADR reports with respect to vulnerable populations. The committee voiced its concern in this respect in its Clinical Trials Report and indicated that greater emphasis must be placed on testing a candidate drug's safety and efficacy in groups that reflect those who can reasonably be expected to consume the drug once it becomes marketed to the general population. However, the committee understands that this may not always be feasible, and in fact, that there will still be limitations on the safety and effectiveness data available for various sub-groups.

The committee shares the concern expressed by some witnesses regarding the uncertainty of whether the current ADR reporting system is effective in detecting safety issues for these sub-groups. Additional mechanisms must therefore be in place to capture this important information. The committee was told of two pieces of legislation in the U.S. intended to improve drug research in the pediatric population. The Pediatric Research Equity Act gives authority to the FDA to require drug companies to conduct pediatric trials on new drugs for adult conditions that can also occur in childhood. The Best Pharmaceuticals for Children Act is voluntary and grants six months additional patent protection where studies have been conducted in children. In Canada, the Act currently provides for an additional six months of market exclusivity when a drug

company has conducted trials in children. With respect to requiring trials in certain populations, the new authority recommended above to require post-approval studies, along with the additional recommendations for optimizing DSEN's research model should help to ensure proper post-approval monitoring for population sub-groups. However, the committee suggests that an additional requirement such as the one contained in the U.S. laws described above that requires safety reviews at specified milestones of a drug's life-cycle would be a suitable for drugs used in children.

The committee suggests that DSEN is well positioned to identify issues among these populations that may need further study but it notes that DSEN cannot act on such concerns as it is not currently permitted to be the source of its own query. Regardless of the barriers, the committee asserts that groups such as children, pregnant and nursing women, and the elderly should not be subject to a lower threshold of drug safety and effectiveness.

**The committee therefore recommends that the Minister of Health direct Health Canada to prioritize the implementation of a post-approval strategy for drug manufacturers and/or the Drug Safety and Effectiveness Network to conduct studies of new drugs in relevant, sub-groups of the population.** [recommendation 12]



**The committee further recommends that the Minister of Health include, within the modernized regulatory framework for drugs proposed in Recommendation 2, a requirement for systematic safety reviews of drugs used in the pediatric population.** [recommendation 13]

**The committee further recommends that the oversight mechanism, established under Recommendation 7, allow for the consideration of issues identified for post-approval studies by the Drug Safety and Effectiveness Collaborating Centres, any of its seven research teams or under the Strategy for Patient-oriented Research as research queries.** [recommendation 14]

## G. ENHANCE COMMUNICATIONS

The committee commends Health Canada on its efforts to improve communications and notes that this is an area that many jurisdictions have yet to perfect. The committee urges Health Canada to continue its efforts to enhance communications, not only the advisories and warnings to consumers and health professionals, but also patient information on the use of drugs and alerts on new or riskier products. With respect to patient information, the committee would like to see standardized information available at the point of sale. Patient information leaflets, PILs, could be one-page inserts derived from a product's monograph, but in a more concise format than the current Part 3, or alternatively, they could be produced in collaboration with the drug manufacturer. Committee believes that PILs must be provided to

the consumer upon receipt of the prescription drug, and should provide information about reporting adverse drug reactions.

**The committee therefore recommends that the Minister of Health direct Health Canada to develop in collaboration with stakeholders and implement within its drug approval process a requirement that all drug submissions and subsequent approvals be accompanied by Patient Information Leaflets, which must provide the Health Canada website and phone number for reporting adverse drug reactions.** [recommendation 15]

**The committee further recommends that the modernized legislative framework proposed in Recommendation 1 include a prohibition on the sale of prescription drugs unless accompanied by a Patient Information Leaflet.** [recommendation 16]

Canada's drug approval and management processes must include a mechanism by which health professionals are alerted to new as well as riskier products. Such an alert can also encourage the reporting of adverse reactions. In this regard, the committee agrees with many witnesses who encouraged adopting labeling requirements like those in the U.S. and the United Kingdom that identify products most likely to be associated with serious ADRs.





**The committee therefore recommends that the Minister of Health implement labeling requirements similar to the United States' 'black box' and the United Kingdom's 'black triangle' to alert health professionals and consumers to new products as well as products that have been linked to serious adverse reactions.**

[recommendation 17]

Finally, the committee would like to see greater transparency in terms of Health Canada's identification of potential safety issues. In this regard it points to the initiative undertaken by the U.S. FDA of posting on its website information about: ongoing investigations, required REMS; detection of safety signals; and post-market studies undertaken.

**The committee therefore recommends greater transparency of Health Canada's post-approval monitoring activities including, but not limited to:**

- a list of the Risk Management Plans that have been submitted;
- a list of identified safety signals and the status of the subsequent assessments; and,
- a list of drugs for which the manufacturer is responsible for post-approval studies, including long-term follow-up.

[recommendation 18]

## H. ADDITIONAL OBSERVATIONS

### Drug Information for Physicians

The committee would like to note its concern regarding the manner by which physicians become informed about approved drugs. According to some witnesses, physicians primarily get this information from the manufacturer or distributor of these products. While the committee acknowledges the legitimate role to be played by the pharmaceutical industry in marketing approved drugs, it also feels that there is a greater role to be played by the regulator. The committee intends to pursue this issue in subsequent phases of this study.

### OAG Report

Health Canada provided this committee with the status of its activities in response to the recommendations made in the Chapter 4 of the Auditor General's November 2011 report entitled *Regulating Pharmaceutical Drugs—Health Canada*. The status report had not been updated since the June 2012 and the committee is concerned that some recommendations have not yet been addressed. In particular, options for implementing stakeholder notification systems about new drug labeling information was to be completed by the end of 2012 and a tracking tool for safety recommendations for all pharmaceuticals is to be completed by March 2013.

**The committee therefore recommends that Health Canada provide assurance that all policies, programs or activities pertaining to monitoring the post-market safety of drugs have been successfully implemented in response to the recommendations from the Auditor General's 2011 report *Regulating Pharmaceutical Drugs—Health Canada*.** [recommendation 19]



## 5. CONCLUSION

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Health Canada has improved its approach to post-approval monitoring of prescription pharmaceuticals in recent years. It has implemented promising initiatives such as the Drug Safety and Effectiveness Network and has worked to improve efficiencies of post-approval monitoring activities within the Marketed Health Products Branch of Health Canada. However, there is still work to be done and the committee believes that Canada must at least keep pace with, and preferably lead, other industrialized nations in its management of prescription pharmaceuticals. Health Canada and the Drug Safety and Effectiveness Network must continue their efforts in this regard. The committee

would like to see this report's recommendations implemented quickly to improve the safety of prescription drugs, to increase transparency in their management, and to foster trust among Canadians in our drug regulatory regime. The committee is convinced that a solid post-approval monitoring program can have a major beneficial impact on the health of Canadians through reduced adverse reactions and improved identification of the appropriate drug use and dosage in population sub-groups.





## APPENDIX A – LIST OF ACRONYMS

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|             |  |              |  |
|-------------|--|--------------|--|
| <b>ADR</b>  | Adverse Drug Reaction                        | <b>NDS</b>   | New Drug Submission                            |
| <b>BGTD</b> | Biologics and Genetic Therapies Directorate  | <b>NOC</b>   | Notice of Compliance                           |
| <b>BPCA</b> | Best Pharmaceuticals for Children Act (U.S.) | <b>NOC/c</b> | Notice of Compliance with Conditions           |
| <b>CIHR</b> | Canadian Institutes of Health Research       | <b>OAG</b>   | Office of the Auditor General                  |
| <b>DIN</b>  | Drug Identification Number                   | <b>PIL</b>   | Patient Information Leaflet                    |
| <b>DSEN</b> | Drug Safety and Effectiveness Network        | <b>PREA</b>  | Pediatric Research Equity Act (U.S.)           |
| <b>EHR</b>  | Electronic health record                     | <b>PSUR</b>  | Periodic Safety Update Report                  |
| <b>EMR</b>  | Electronic medical record                    | <b>REMS</b>  | Risk Evaluation and Mitigation Strategy (U.S.) |
| <b>FDA</b>  | Food and Drug Administration (U.S.)          | <b>RMP</b>   | Risk Management Plan                           |
| <b>HPFB</b> | Health Products and Food Branch              | <b>SPOR</b>  | Strategy for Patient-oriented Research         |
| <b>MHPD</b> | Marketed Health Products Directorate         | <b>TPD</b>   | Therapeutic Products Directorate               |
|             |  | <b>U.S.</b>  | United States                                  |



## APPENDIX B – LIST OF RECOMMENDATIONS

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### RECOMMENDATION 1

The committee therefore recommends that the Government of Canada introduce legislation which includes authorities for drug management. These authorities should include, but not be limited to:

- The authority to require post-approval studies;
- The authority to require label changes;
- The authority to require re-assessment of a drug's safety and effectiveness;
- The authority to disclose publicly information about a drug's risks or benefits;
- The authority to require Risk Management Plans and Periodic Safety Update Reports; and
- The authority to issue mandatory drug recalls.

### RECOMMENDATION 2

The committee therefore recommends that the Minister of Health ensure publication of a modernized regulatory framework for drugs that applies a life-cycle approach to drug management in the *Canada Gazette*, beginning in 2013.

### RECOMMENDATION 3

The committee further recommends that long-term studies of drug safety must be included as part of a life-cycle approach to drug management.

### RECOMMENDATION 4

The committee therefore recommends that the Minister of Health work to achieve equal funding for both pre- and post-approval drug regulatory activities and ensure that post-approval resources are adequate for implementation of a comprehensive life-cycle approach to drug management.

### RECOMMENDATION 5

The committee therefore recommends that the Minister of Health order a comprehensive and independent assessment of the work of the Drug Safety and Effectiveness Network (DSEN) and that a report be submitted to the President of the Canadian Institutes of Health Research (CIHR) as well as to the Minister of Health and be made publicly available. The report should provide:

- An analysis of DSEN's ability to operate independently from both CIHR and Health Canada;
- A recommendation of DSEN's budgetary needs in order to conduct the necessary post-approval studies;
- A discussion of the findings that DSEN has conveyed to Health Canada and how these have been acted upon by the regulator;
- A comparison of DSEN's performance relative to other international post-approval drug research networks; and
- Advice on whether DSEN should be re-structured in order to best fulfill its mandate.

### RECOMMENDATION 6

The committee further recommends that the Minister of Health provide assurance that the Drug Safety and Effectiveness Network is:

- a permanent entity with on-going and sustained funding; and
- responsible for its own budget.



## RECOMMENDATION 7

The committee further recommends that the Minister of Health establish an oversight mechanism to regularly review the findings of the Drug Safety and Effectiveness Network and make this information publicly available.

## RECOMMENDATION 8

The committee therefore recommends that the Drug Safety and Effectiveness Network:

- incorporate the model used by the Canadian Pharmacogenomics Network for Drug Safety as a means to apply active post-approval surveillance to adverse drug reaction reporting and,
- make use of the research network capacity proposed in the committee's clinical trials report of November 2012.

## RECOMMENDATION 9

The committee therefore recommends that the Minister of Health meet with provincial and territorial counterparts to discuss implementation of a system similar to British Columbia's PharmaNet in all jurisdictions in order to capture data on all prescription drugs dispensed.

## RECOMMENDATION 10

The committee further recommends that the Minister of Health urge provincial and territorial counterparts, through the work of Canada Health Infoway, that the national system of electronic health records must be linkable to and compatible with the electronic system that captures data on dispensed prescription drugs.

## RECOMMENDATION 11

The committee therefore recommends that the Minister of Health ensure that Health Canada is represented at ongoing federal/provincial/territorial discussions regarding the implementation of electronic medical records and electronic health records to promote the inclusion of the adverse drug reaction reporting form.

## RECOMMENDATION 12

The committee therefore recommends that the Minister of Health direct Health Canada to prioritize the implementation of a post-approval strategy for drug manufacturers and/or the Drug Safety and Effectiveness Network to conduct studies of new drugs in relevant, sub-groups of the population.

## RECOMMENDATION 13

The committee further recommends that the Minister of Health include, within the modernized regulatory framework for drugs proposed in Recommendation 2, a requirement for systematic safety reviews of drugs used in the pediatric population.

## RECOMMENDATION 14

The committee further recommends that the oversight mechanism, established under Recommendation 7, allow for the consideration of issues identified for post-approval studies by the Drug Safety and Effectiveness Collaborating Centres, any of its seven research teams or under the Strategy for Patient-oriented Research as research queries.

## RECOMMENDATION 15

The committee therefore recommends that the Minister of Health direct Health Canada to develop in collaboration with stakeholders and implement within its drug approval process a requirement that all drug submissions and subsequent approvals be accompanied by Patient Information Leaflets, which must provide the Health Canada website and phone number for reporting adverse drug reactions.



### RECOMMENDATION 16

The committee further recommends that the modernized legislative framework proposed in Recommendation 1 include a prohibition on the sale of prescription drugs unless accompanied by a Patient Information Leaflet.

### RECOMMENDATION 17

The committee therefore recommends that the Minister of Health implement labeling requirements similar to the United States' 'black box' and the United Kingdom's 'black triangle' to alert health professionals and consumers to new products as well as products that have been linked to serious adverse reactions.

### RECOMMENDATION 18

The committee therefore recommends greater transparency of Health Canada's post-approval monitoring activities including, but not limited to:

- a list of the Risk Management Plans that have been submitted;
- a list of identified safety signals and the status of the subsequent assessments; and,
- a list of drugs for which the manufacturer is responsible for post-approval studies, including long-term follow-up.

### RECOMMENDATION 19

The committee therefore recommends that Health Canada provide assurance that all policies, programs or activities pertaining to monitoring the post-market safety of drugs have been successfully implemented in response to the recommendations from the Auditor General's 2011 report *Regulating Pharmaceutical Drugs—Health Canada*.



## APPENDIX C – WITNESSES

### Wednesday, October 3, 2012

|   |   |
|---|---|
| Health Canada                           | Berthiaume, Dr. Marc, Director, Marketed Health Products Directorate (HPFB)     |
|   | Glover, Paul, Assistant Deputy Minister, Health Products and Food Branch (HPFB) |
| Office of the Auditor General of Canada | Maxwell, Neil, Assistant Auditor General  |
|   | Dubé, Louise, Principal   |

### Wednesday, October 17, 2012

|  |   |
|--|---|
| Canadian Institutes of Health Research | Beudet, Dr. Alain, President  |
|  | Peterson, Dr. Robert, Executive Director, Drug Safety and Effectiveness Network     |
|  | Young, Terence, Member of Parliament for Oakville and founder of Drug Safety Canada |
| Psychiatric Medication Awareness Group | Currie, Janet, Representative   |

### Wednesday, October 24, 2012

|   |   |
|---|---|
| Canadian Medical Association                            | Reid, Dr. Anna, President                             |
|   | Toombs, Millicent, Director, Public Health Department |
| Canadian Nurses Association                             | Mildon, Barbara, President                            |
| National Association of Pharmacy Regulatory Authorities | Bouchard, Carole, Executive Director                  |

### Thursday, October 25, 2012

|   |   |
|---|---|
| BIOTECanada                                 | Casey, Andrew, President and Chief Executive Officer  |
|   | Del Bosco, Loretta, Director, Regulatory Affairs, Quality Assurance and Operations, Abbott Canada |
| Canadian Generic Pharmaceutical Association | D’Cunha, Dr. Colin, Director, Global Medical Affairs, Apotex Inc.                                 |
| Rx&D  | Glezer, Stan, Vice-President, Evidence, Value and Access, Sanofi                                  |
|   | Hughes, Ken, Vice-President, Scientific and Regulatory Affairs                                    |
|   | Robinson, Walter, Vice President, Government Relations  |



### Wednesday, October 31, 2012

United States Food and Drug Administration

Dal Pan, Dr. Gerald, Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research

Temple, Robert, Dr. Robert Temple, Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research

### Wednesday, November 7, 2012

Canada Health Infoway

Sheridan, Mike, Chief Operating Officer

Zelmer, Jennifer, Senior Vice-President, Clinical Adoption and Innovation

Health Council of Canada

Abbott, John G., Chief Executive Officer

Sketris, Ingrid, Councillor

Institute for Safe Medication Practices Canada

Hyland, Sylvia, Vice-President

### Thursday, November 8, 2012

As individuals

Baylis, Françoise, Professor and Canada Research Chair, Faculty of Medicine, Dalhousie University

Lemmens, Trudo, Scholl Chair in Health Law and Policy, Faculty of Law, University of Toronto

Wiktorowicz, Mary, Chair and Associate Professor, School of Health Policy & Management, Faculty of Health, York University

### Wednesday, November 21, 2012

As individuals

Carleton, Bruce, Professor and Co-Chair, Division of Translational Therapeutics, Department of Pediatrics, University of British Columbia

Tamblyn, Robyn, Scientific Director, Department of Medicine, Department of Epidemiology, Biostatistics and Occupational Health, McGill University







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