

January 2014



PRESCRIPTION PHARMACEUTICALS IN CANADA

Off-Label Use

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 19, 2013:

The Honourable Senator Ogilvie moved, seconded by the Honourable Senator Runciman:

That the Standing Senate 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 papers and evidence received and taken and work accomplished by the committee on this subject during the First Session of the Forty-first Parliament be referred to the committee; and

That the committee submit its final report no later than December 31, 2014 and that the committee retain until March 31, 2015, all powers necessary to publicize its findings.

After debate,

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:

Diane Bellemare, Maria Chaput, Jane Cordy, Lillian Eva Dyck, Nicole Eaton, Tobias Enverga, Hugh Segal, Judith Seidman, Asha Seth, Carolyn Stewart Olsen

Ex Officio Members:

The Honourable Senators Claude Carignan, P.C. (or Yonah Martin) and James Cowan (or Joan Fraser).

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

The Honourable Senators Campbell, Demers, Oh, Mercer, Munson, Raine and Verner.

Parliamentary Information and Research Services, Library of Parliament:

Sonya Norris, Analyst.

Clerk of the Committee:

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INTRODUCTION

The Standing Senate Committee on Social Affairs, Science and Technology (“committee”) is undertaking a four-phase study on prescription pharmaceuticals, as described in the Order of Reference adopted on November 22, 2011. The committee tabled reports on the first two phases of this study in November 2012 and March 2013. These reports were entitled *Canada’s Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* (the “Clinical Trials Report”) and *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring of Safety and Effectiveness* (the “Post-Approval Monitoring Report”), respectively.¹ A new order of reference was adopted on 19 November 2013 which re-established the four-phase study at the beginning of the second session of the 41st parliament.

Between February 27 and April 17, 2013, the committee heard from witnesses in regard to the third phase of this study, the “off-label” use of prescription pharmaceuticals. Over the course of seven meetings, the committee heard testimony from physicians most involved with off-label prescribing; academics and researchers with an interest in pharmaceutical policy; representatives of the drug manufacturing industry and the Canadian Agency for Drugs and Technologies in Health; patient advocates; and officials from Health Canada and the Canadian Institutes of Health Research.



¹ For more detail refer to the Standing Senate Committee on Social Affairs, Science and Technology’s 14th and 20th reports, which pertain to the first two phases of the prescription pharmaceutical study.



CONTEXT

OFF-LABEL USE OF PRESCRIPTION DRUGS

As this committee has discussed in the first two reports of its study, all prescription pharmaceuticals (“drugs”) must be approved for sale by Health Canada. This process is sometimes also referred to as market authorization. When Health Canada approves a drug for sale the approval stipulates, among other things; the population for whom the drug can be prescribed, the indication(s) the drug can treat, and the dosage(s) that can be administered.² The use of an approved drug beyond the criteria set out in the product’s approval is referred to as “off-label” use.

Label, as defined in the *Food and Drugs Act*, means: “any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package.”³ Under the *Food and Drug Regulations*, labels can be described as inner and outer labels. The inner label is “the label on or affixed to an immediate container of a food or drug” while the outer label is “the label on or affixed to the outside of a package of a food or drug.”⁴ Health Canada considers the product monograph, which includes information about the approved indications, dosages and population groups, as part of a product’s outer labelling.⁵

As described in the previous reports for the first two phases of this study, drug approval is based on the specifics sought by the manufacturer in its New Drug Submission (NDS) or abbreviated new drug submission (ANDS) for generic drugs and for which clinical trial data or bioequivalency data have been provided, respectively. Frequently, approved drugs are used in a broader population, for different indications or at different dosages than have been approved by

Health Canada. This off-label use is widespread and has both advantages and disadvantages. While not in itself prohibited, but rather considered a “practice of medicine” issue, manufacturers are prohibited from promoting off-label use of their products.

HEALTH CANADA’S ROLE

All drugs must be approved by Health Canada before they can be sold in this country. Health Canada’s approval is conducted within the Therapeutic Products Directorate and takes into account such factors as: the method of manufacture, chemistry, therapeutic claims and associated risks. Upon approval, should Health Canada determine that the benefits outweigh the risks associated with a drug’s use, Health Canada issues a Notice of Compliance (NOC) and a Drug Identification Number (DIN) to allow it onto the Canadian market. The indications, or illnesses, for which a drug is approved, appear on the drug’s label, specifically the product monograph. Additionally, the monograph sets out the instructions for optimal use including dosing information and route of administration, as well as the population group for which the drug has received approval and conditions under which the drug should not be used (“contra-indications”).

While Health Canada has the authority to conduct post-approval monitoring of approved drugs to ensure continued compliance with the *Food and Drugs Act* and its regulations, it does not have jurisdiction over the prescribing practices of physicians, which is provincially/territorially regulated. Health Canada’s authority is limited to post-market surveillance of safety and efficacy as well as advertising of drug products. With respect to post-market surveillance, the Post-Approval

² The conditions of approval also include specifics regarding the product’s formulation, the method of manufacture, etc. to which the manufacturer must adhere. These criteria are beyond the control of the end-user and are not considered among the variables to which off-label use is subject.

³ *Food and Drugs Act*, s.2.

⁴ *Food and Drug Regulations*, A.01.010.

⁵ Health Canada, *Product Information (labelling)*.



Monitoring Report describes Health Canada's role in assessing reports of adverse drug reactions (ADR) and, should it discover safety signals, issuing risk communications. However, ADR reports do not necessarily distinguish between on and off-label use.

While there is no federal prohibition against the off-label prescribing of approved drugs, section 9(1) of the *Food and Drugs Act* states that:

“No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.”

As such, manufacturers cannot promote⁶ off-label use of their products “because the terms of such authorization have not been established and the proposed indication(s) for use have not been verified.”⁷ With respect to advertising, all direct to consumer advertising of prescription pharmaceuticals is prohibited, except for advertisements that are limited only to providing information regarding a product's name, price and quantity.⁸ Drug manufacturers may advertise directly to health professionals through targeted publications.

PROVINCIAL/TERRITORIAL ROLE

The practice of medicine is subject to regulation by the provinces and territories and much of it is entrusted to the medical bodies to self-regulate. Generally, physicians are at liberty to prescribe in a manner that is in their patients' best interests. Physicians and pharmacists are responsible for informing patients about the potential side effects of the drugs that are prescribed to them and for discussing drug interactions and contraindications. In principle, off-label prescribing should be

appropriate and accompanied by disclosure of any additional relevant information.

Reimbursement of drugs prescribed for off-label indications through publicly funded provincial/territorial drug plans may not be consistent across jurisdictions. The Canadian Agency for Drugs and Technologies in Health (CADTH) conducts cost-benefit assessments of drugs for their approved indications through its Common Drug Review (CDR) process and then issues a recommendation to provinces and territories (except Quebec) as to whether the drug should be reimbursed by public programs. However, jurisdictions are not obliged to adopt CDR recommendations.

OVERVIEW OF THE CANADIAN SITUATION

It is important to acknowledge that there are different categories of off-label drug prescribing when considering its prevalence. Rare diseases, those that affect fewer than one in 2000 individuals, are most commonly treated with off-label uses of prescription drugs because few drugs have been developed specifically to treat many of the rare diseases. This situation leads researchers and health professionals to find innovative uses for existing drugs.

Despite the prevalence of off-label drug use for rare disorders, this category represents only a small proportion of all off-label prescriptions, although few studies have assessed the extent of off-label prescribing in Canada. However, the committee was told of a recent study conducted in Quebec that suggested 11% of all drugs prescribed are for conditions that are not covered by the regulatory approval for the drugs from Health Canada.⁹ The study also found that 79% of the off-label prescriptions lack strong scientific evidence of efficacy.¹⁰

⁶ Section 2 of the *Food and Drugs Act* defines advertisement broadly to include both direct and indirect promotion for the purpose of selling a drug.

⁷ Health Canada, “Guidance Document – Health Canada and Advertising Preclearance Agencies' Roles Related to Health Product Advertising,” 2010.

⁸ *Food and Drug Regulations*, C.01.044.

⁹ Tewodros Eguale et al., “Drug, Patient, and Physician Characteristics Associated With Off-label Prescribing in Primary Care,” *Archives of Internal Medicine*, vol. 172, no. 10, May 28, 2012, pp. 781-788.

¹⁰ The study defined strong evidence as including: 1) drug effectiveness in treating a particular condition, 2) all or almost all patients with the condition are recommended the drug, and 3) there is at least one randomized, controlled trial used to evaluate the drug's efficacy.



In addition to prescribing for conditions not included in the regulatory approval for the drugs in question, off-label use also includes prescribing to sub-groups of the population that may not be included in the approval. As stated above, the product monograph sets out the population group for which the drug has received market authorization in Canada. Both the Clinical Trials report and the Post-Approval Monitoring Report describe the lack of clinical evidence of safety and efficacy for certain sub-groups of the population. These sub-groups include children, the elderly and, pregnant and nursing women. Often there is no specific information about a drug's safety and efficacy for patients less than 18 years of age. As a result, as reported by this committee in its Clinical Trials Report, over 75% of medicines prescribed to the pediatric population are prescribed off-label. Similar situations were described for the elderly population and for pregnant and nursing women, sub-groups usually omitted from clinical trials.

BALANCING INNOVATIVE DRUG USE WITH PATIENT SAFETY

Off-label prescribing is not prohibited in Canada. In fact, as several witnesses described, it is essential so that health professionals can pursue treatment that is in the best interest of their patients. There are many examples of innovative uses for existing drugs, uses that may not have

been the original intent for these drugs. Treatment for rare diseases is a prime example of such innovation. Other instances of off-label drug use pertain to the treatment of conditions that may be very similar in terms of symptomology or physiology as the condition for which the drug has approval. For example, a cancer drug that has received approval for a specific type and stage of cancer may prove to be suitable for additional oncological purposes. The same may be true for population groups that were not included in the original clinical trials. For example, a cholesterol lowering drug that was not tested in the elderly for a variety of reasons before receiving market authorization may prove to be safe and effective in that sub-group of the population. Finally, exhausting the inventory of traditional available treatments can be the inspiration for off-label prescribing. A physician left with no on-label treatment options for a patient, or a drug plan seeking to find cost-savings, can benefit from innovative uses of approved prescription drugs.

Potential benefits of off-label drug use need to be balanced with the potential risks, however. As such, information about the safety and effectiveness of drugs when they are used off-label should be collected, analysed and shared. In this way a comprehensive risk-benefit assessment can be conducted for off-label uses.





OFF-LABEL DRUG USE - ISSUES OF CONCERN

THE EXTENT OF OFF-LABEL USE IN CANADA

The prescribing of drugs by health professionals is a practice of medicine issue and is not subject to federal oversight. Once approved for sale in this country by Health Canada, drugs can be prescribed to whomever, for whatever purpose and in the dosage that is determined by the health professional to be in the best interest of their patients. Several witnesses noted that considerable benefit has been realized because of this freedom. Many drugs are thought to be safe and effective in sub-groups of the population that were not included in early testing of the drugs. Many drugs are believed to be safe and effective to treat conditions for which they have not received Health Canada approval. Still others are assumed to be just as safe and effective in dosages different from those set out in their product monographs. However, without formal, structured studies to examine the safety and efficacy of approved drugs for off-label purposes, there is an unknown level of risk involved when patients are prescribed drugs for off-label use. For this reason, the extent of off-label prescribing is a concern.

As mentioned above, several witnesses discussed a recent study that found 11%, or one in nine, prescriptions were for an off-label indication. Off-label prescribing associated with population group or dosing were not measured in the study. The study followed 113 physicians practising in urban centres in Quebec whose offices are equipped with MOXXI, the Medical Office of the 21st Century, electronic health record (EHR) research network program. MOXXI includes electronic prescribing. With respect to the safety

and effectiveness, the researchers reported that 79% of the off-label prescriptions were not supported by strong scientific evidence. Strong scientific evidence was defined as including at least one randomized, controlled clinical trial (RCT). The study also found that central nervous system drugs were prescribed off-label 26% of the time, anticonvulsants were prescribed off-label 67% of the time, antipsychotics 44% of the time and antidepressants 33% of the time. Quinine, an antimalarial, was found to be prescribed off-label 99.5% of the time for nocturnal leg pain with no strong scientific evidence to support that use. Quinine is associated with serious ADRs and Health Canada issued a warning against this off-label use in April 2011.¹¹ Gabapentin, an antiepileptic, was shown to be prescribed off-label 99.2% of the time for indications including pain and fibromyalgia. Of particular concern, this study measured a 43% increase in ADRs for off-label use over on-label use of prescription drugs.

The committee also heard about the reasons for off-label prescribing. With respect to off-label indications, witnesses spoke of the need to expand on the indications listed for oncology drugs. Dr. Kara Laing of the Canadian Association of Medical Oncologists explained that oncology drugs are often approved for a specific cancer site or cancer stage. Frequently there is considerable evidence to suggest that the indications for use can be broadened to another site or a different stage of development. As such, oncologists were described as being “very comfortable” with most of their off-label decisions. Off-label use in oncology also often occurs when there is an uncommon tumour for which there may not be an approved

¹¹ Canadian Adverse Reaction Newsletter, “Quinine sulfate and serious adverse reactions,” vol. 21, issue 2, April 2011.



drug, or the response to the approved drug has not been satisfactory. Rare diseases make up another category of off-label indications for prescription drug use. The committee was told that as much as 80% of prescriptions for rare diseases are off-label because so few medicines have been approved specifically to treat these conditions.

With respect to off-label prescribing associated with sub-groups of the population, witnesses reiterated the concerns that this committee heard during the previous two phases of this study that prescribing to children, older Canadians and women, particularly pregnant and nursing women, is often off-label because clinical trials do not usually include these populations and the Health Canada approval may not extend to them. This aspect of off-label drug use is discussed below under “Vulnerable Sub-Groups of the Population.”

Several witnesses discussed the profile of those drugs that tend to be most frequently prescribed off-label. In this regard the committee heard that older drugs, which have been on the market longer thus allowing the opportunity to discover new uses, are more likely to be prescribed off-label than newer drugs. It was also emphasized by many witnesses that older drugs are also off-patent with generic versions on the market. As such, there is little financial incentive for the original drug manufacturer to apply to Health Canada for changes to the product monograph.

VULNERABLE SUB-GROUPS OF THE POPULATION

Children

As is the case with off-label prescribing in general, there are few data available on the prevalence of the practice with respect to prescribing to those under 18 years of age. Anne Rowan-Legg of the Canadian Pediatric Society told the committee that information from 2003 suggested that the average child was prescribed four medications per year but

she stated that the use of medication in children has increased since then. Dr. Stuart MacLeod, a professor with the Child & Family Research Institute stated that 75% of medications prescribed to children are off-label because those medicines have not been appropriately studied in the pediatric population, although adolescents have been included in clinical trials more often than younger children. In terms of the proportion of prescriptions that are off-label in pediatric medicine the committee was told that 25% of outpatient and up to 60% of in hospital prescribing is off-label.

Of particular concern to several witnesses are the second generation antipsychotics, which are among the most frequently prescribed drugs for behavioural issues associated with a variety of conditions including attention deficit/hyperactivity disorder, autism spectrum disorder and disruptive behaviour disorder in very young children. This class of drug, which is approved only for conditions such as bipolar disorder and schizophrenia, has not been approved for use in young children. Health Canada has warned of serious ADRs associated with the use of these antipsychotics by children and adolescents.¹² The committee was told that use of antipsychotics, as well as anticonvulsants and antidepressants, has increased dramatically in the last ten years.



¹² Canadian Adverse Reaction Newsletter, “Second-generation antipsychotics and cardiometabolic adverse reactions in children and adolescents,” vol. 22, issue 1, January 2012.



The committee heard that health professionals often have no product information specific for patients under 18 about a drug's effectiveness for a specific condition, appropriate dosing or side effects and safety risks. As such, decisions are based on extrapolation of adult studies which is not appropriate since children are not simply little adults. The Canadian Paediatric Surveillance Program, an initiative of the Canadian Paediatric Society, aims to fill some of this knowledge gap by actively seeking ADR information from 2,500 pediatricians across Canada.

Health Canada officials emphasized that the department has taken steps to try to improve knowledge of the risks and benefits associated with medications prescribed to children. The committee heard that Health Canada worked with the Canadian Paediatric Society to create the Canadian Paediatric Surveillance Program as a means of promoting the collection of safety information on drugs used in treating children. Officials also pointed to the Pediatric Expert Advisory Committee, which was created in 2009 to provide advice to Health Canada in the development, licensing and post-approval monitoring of drugs. However, no examples were provided about the advice that has been offered by the expert committee or how it has been used to inform the knowledge base of the safety and effectiveness of pediatric drugs.



Finally, officials referred to the six-month data protection extension which is granted to drug manufacturers who conduct clinical trials in the pediatric population. This extension provides an additional six months of market exclusivity to a new drug before generic versions can be approved for sale. This extension was implemented within the *Food and Drug Regulations* in 2006, however since that time only 25 products have been granted the extension. The committee was told that perhaps the incentive of longer market exclusivity is in itself not sufficient to encourage clinical trials in the pediatric population. The approach in the United States, as described in the Post-Approval Monitoring Report, is two-fold; the *Best Pharmaceuticals for Children Act*, which is voluntary and grants six months of additional patent life to drugs tested in children, and the *Pediatric Research Equity Act*, which authorizes the Food and Drug Administration to require drug makers to conduct trials in children.¹³ The committee heard, in contrast to Canada's 25 pediatric drugs the U.S. has approved over 200, and that therefore both strategies may be needed in order to substantially improve pediatric drug research.

Women

The committee was told by Dr. Jennifer Blake of the Society of Obstetricians and Gynaecologists of Canada, that there is no disagreement that there are important physiological differences that affect how women will respond to medications, particularly pregnant and nursing women and that the unique needs of women should be addressed in drug testing, even testing of generic drugs. These concerns were raised in the clinical trials and post-approval monitoring phases of the committee's study. Several medications that are used by women, particularly pregnant and nursing women, have not been tested in those populations and therefore their use is off-label when prescribed. As such, the practice of medicine regularly requires

¹³ Standing Senate Committee on Social Affairs, Science and Technology, "Prescription Pharmaceuticals in Canada: Post-Approval Monitoring of Safety and Effectiveness," 2013, page 23.



off-label prescribing. Unfortunately, some women may consider that it is more prudent not to consume a prescribed medication because of the lack of safety and efficacy data, and this may not necessarily be the case. Witnesses emphasized that a lack of safety and efficacy data does not mean that a drug is unsafe or ineffective. The means of collecting that data, however, in this population may not be through the traditional RCTs that are required by Health Canada for market approval.



Seniors

Similar to the population sub-groups described above, the elderly are often not included in RCTs. In addition to changes in the metabolism of older individuals, which has an impact on the way the body responds to and processes medicines (pharmacokinetics and pharmacodynamics), frequently seniors also suffer from multiple conditions and may be prescribed several medications. These factors complicate the design of RCTs and could mask both benefits and risks associated with the drug in question. Allan Huang of the Canadian Geriatrics Society told the committee that RCTs may not be the most appropriate way to collect safety and effectiveness data from this population group.

The committee was told that prescribing to seniors is often off-label, not only because they are part of a sub-group not included in RCTs but also for off-label indications. Witnesses stated that as much as one-third of long-term care residents are prescribed antipsychotics. Frequently antipsychotics are prescribed to treat behavioural issues associated with dementia but the committee heard that of the three widely used antipsychotics, only one has been approved for that purpose. Witnesses also revealed that there have been several warnings issued by the drug regulators in both the United States and Canada about serious adverse reactions associated with antipsychotic drug use by older adults with dementia. They indicated however that these warnings have had little effect on prescribing practices, possibly because they have provided little information about prescribing alternatives.



DRUGS USED TO TREAT RARE DISEASES

Off-label drug prescribing and use for rare diseases was described to the committee as being the rule as opposed to the exception. As much as 80% of prescriptions for rare diseases are off-label because there are so few drugs that have been specifically developed to treat any rare diseases. The committee was told that a study by Europe's organization for



rare diseases, EURORDIS, reported that over 100 medications are prescribed off-label for 90 rare diseases. Witnesses spoke of the limitations for research and development in this area, namely that there is little financial incentive for companies to invest in developing medicines for relatively small markets and that in the eventuality that a drug is developed, there is a very small population in which clinical trials can be conducted. This committee discussed these limitations in its Clinical Trials Report.

In some instances, effective off-label treatments have been identified for rare conditions. Unfortunately, access to treatment is inconsistent across the country. Maureen Smith, of the Canadian Organization for Rare Disorders, informed the committee that some provincial drug formularies will reimburse the cost of some drugs used for the off-label treatment of rare diseases while others will not. Additionally, some drug manufacturers have compassionate access programs and provide medicines at reduced or no cost while others do not. The issue of access is discussed under “Access to Medicines.”

SAFETY AND EFFECTIVENESS DATA

Witnesses spoke frequently of the potential benefits of prescribing prescription drugs for off-label indications and sub-groups of the population; however, the need to continue collecting safety and effectiveness data was also emphasized repeatedly. In fact, the ongoing assessment of safety and effectiveness is one of the key aspects of a life-cycle approach to drug management that Health Canada has indicated it is implementing and which the committee recommended in its Post-Approval Monitoring Report. Various ways of collecting safety and effectiveness data were described by witnesses.

First, the reporting of ADRs, which was extensively addressed in the Post-Approval Monitoring Report, with respect to the off-label use of drugs was

described by many witnesses as requiring more effort. Health Canada suggested that the existing mechanism for reporting ADRs to the department is sufficient because it captures both on-label and off-label use. However, some witnesses pointed out that ADRs for a particular drug may be specific to a particular population group or to those taking a drug for an off-label indication. For example, Tewodros Eguale of the Clinical and Health Informatics Group at McGill University stated that his research had reported a 43% increase in ADRs for off-label drug use over on-label use. Witnesses noted that it is not mandatory to fill out several of the fields in an ADR report including the age of the patient and the condition for which he or she has been prescribed the medicine. The committee was told that ADR reports should require sufficient information to determine off-label use.

Canada has no process in place for monitoring off-label drug use. The ADR reporting process has the potential to alert officials to safety signals only, not effectiveness issues. Jeff Poston, President of the Canadian Pharmacists Association, told the committee that there is no formal mechanism for recording and monitoring the effectiveness of drugs used off-label. As such, several witnesses commented on the best way to generate the needed data. The committee was told many times that the traditional RCTs may not be appropriate in certain sub groups or for rare diseases. It heard that other types of research studies could provide the evidence needed to assess a drug’s benefit/risk profile. In this regard, Trudo Lemmens, Scholl Chair in Health Law and Policy at the University of Toronto, described the hierarchy of scientific and clinical evidence placing meta-analyses of randomized controlled trials and individual RCTs at the top, followed by non-randomized clinical trials or other interventional studies, observational studies from administrative data and finally, expert opinion.



Despite there being no formal mechanism to monitor safety and effectiveness of off-label drug use, the committee heard that Canada has the capacity to do so. Robyn Tamblyn, Scientific Director at McGill University Health Centre's Research Institute, emphasized that Health Canada has an obligation to monitor the safety of all approved drugs including those used off-label and also pointed out that the infrastructure is in place to do so. Paula Rochon, a senior scientist with the Institute for Clinical Evaluative Sciences, stated that substantial administrative data is already collected to conduct the necessary observational studies. In this regard, many witnesses referred to the Drug Safety and Effectiveness Network (DSEN) within the Canadian Institutes of Health Research (CIHR) to conduct the needed studies.

AWARENESS AND PROMOTION OF OFF-LABEL USES

The committee heard from several witnesses about physician and patient awareness regarding off-label prescription drug use. In cancer treatment, as discussed above, drugs are often used for off-label purposes and oncologists are quite comfortable with these decisions. Witnesses explained that off-label use is limited by reimbursement decisions. Older oncology drugs, which tend to be used off-label more frequently than the newer ones, must be approved for the requested use by the province or within the hospital in which they are used. The committee heard that the approval mechanism varies among provinces but for many it includes a panel that reviews the existing literature. Hospitals will sanction only the use of oncology drugs that have been approved through their jurisdiction's established process. With respect to new oncology drugs, witnesses described the pan-Canadian Oncology Drug Review (pCODR) which assesses the products from a cost-benefit perspective and makes recommendations to the provinces and territories (except Quebec) about whether to fund them. In Quebec, the Institut national d'excellence

en santé et en services sociaux (INESSS) conducts these assessments. This mechanism is described further under "Improve Assessments."

Other representatives of physician organizations also indicated that they are largely aware when prescribing drugs for off-label purposes but that they limit such prescribing to when it is in the best interest of the patient and only once they have done due diligence in assessing the literature and the experience of colleagues. In contrast to this situation, however, the committee heard from several witnesses that physicians are often unaware that they are prescribing off-label and that a lot of the knowledge that physicians have about medicines has been acquired through sales representatives from pharmaceutical companies. In this regard, evidence was presented from a recent study that off-label indications for drugs were mentioned to primary care physicians from two Canadian cities by pharmaceutical sales representatives in 13% of drug-specific promotions.¹⁴

Several witnesses commented on the difficulty of finding comparative information on drug safety and effectiveness. Canada's Compendium of Pharmaceuticals and Specialties (CPS) is a primary source for information about approved drugs in Canada. The CPS is produced by the Canadian Pharmacists Association and is a



¹⁴ Barbara Mintzes et al., "Pharmaceutical Sales Representatives and Patient Safety: A comparative Prospective Study of Information Quality in Canada, France and the United States," *Journal of General Internal Medicine*, April 2013, DOI: 10.1007/s11606-013-2411-7.



compilation of approved pharmaceuticals that provides product monograph information for each product. The CPS does not, however, provide any information that compares drugs for the same indications or any information about off-label uses. In this regard, Joel Lexchin, a professor at the School of Health Policy and Management at York University, told the committee about the *Australian Medicines Handbook*. This document provides concise comparative drug information and is assembled by the national Australian associations for general practitioners, pharmacists and, pharmacologists and toxicologists. The *British National Formulary* was similarly described although it is produced in conjunction with the Department of Health as well as the medical practitioner and pharmacist associations.

While the committee heard that some physicians make decisions about off-label prescribing only after reviewing the existing literature, others, including Health Canada, emphasized that it is unreasonable to expect prescribers to undertake such exhaustive analyses. Witnesses indicated that physicians don't have full access to the *Cochrane Database of Systematic Reviews*, which provides assessments of the existing research literature to establish whether or not there is acceptable evidence about the safety and efficacy of a specific treatment.

Representatives of the pharmaceutical industry emphasized that section 9(1) of the *Food and Drugs Act* prohibits drug manufacturers from advertising their products beyond the specifics established in the product monographs and that the manufacturers' Codes of Conduct and Ethical Practices reinforce this prohibition. Under the Act, advertisement is broadly defined as anything done, either directly or indirectly, to promote the sale of a drug. The representatives stated, however, that there is a fine line between the exchange of information and promotion. Janet Currie, of the Psychiatric

Medication Awareness Group, discussed the role of pharmaceutical sales representatives with respect to physician awareness of off-label prescribing and suggested that the penalties associated with the prohibited activity are not sufficiently harsh to discourage it. In this regard, some witnesses suggested that Canada might benefit from legislation similar to that in the United States known as whistle-blower legislation. Under the U.S. *False Claims Act* private parties can file actions alleging that the federal government has been defrauded. If the suit succeeds, the private party may receive up to 30% of the government's award.

INFORMED CONSENT

The issue as to whether there should be an obligation on the part of the prescribing physician to specify that a drug is being prescribed off-label was raised a number of times during the course of this study. The obligation would involve either indicating on the prescription that it would be for off-label use, or that the prescriber obtain informed consent from their patient for the off-label prescription. The committee heard suggestions such as writing "off-label" on the prescription itself and discussing the prescribed drug with the patient to outline that it has not been formally assessed for the prescribed purpose. Jitender Sareen, Chair of the Research Committee of the Canadian Psychiatric Association, indicated that these suggestions are in line with guidelines issued by the Canadian Medical Protective Association (CMPA). The CMPA makes these recommendations to physicians in order to minimize the medico-legal risks of prescribing off-label because of the "uncertainty about the efficacy of the drug or product, and possible adverse reactions."¹⁵

Witnesses acknowledged that implementing such requirements would fall exclusively within provincial jurisdiction. Even so, implementing them would be problematic since physicians often don't know that they are prescribing off-label and

¹⁵ Canadian Medical Protective Association, "Risk management when using drugs or medical devices off-label," September 2012.



enforcement of the requirements would be difficult. Witnesses also suggested that there would be no value and that nothing would change if these requirements were implemented unless it was linked to ADR and effectiveness reporting. They stressed that it is more important to ensure that safety and effectiveness are optimized.

ACCESS TO MEDICINES

Access to prescription drugs may be inconsistent among jurisdictions across Canada. For individuals who rely on publicly funded drug plans, drugs that are prescribed off-label may or may not be reimbursed. The Canadian Agency for Drugs and Technologies in Health (CADTH) is responsible for conducting, under its Common Drug Review, cost-benefit analyses of most new drugs approved by Health Canada. It then provides formulary listing recommendations to Canada's publicly funded drug plans (except Quebec). As described earlier, this responsibility is fulfilled by INESSS in Quebec.

CADTH also conducts other assessments including therapeutic reviews of old drugs and optimal use projects when requested by federal, provincial or territorial health ministries, health authorities, hospitals and health care programs. Drugs for cancer treatment are assessed through pCODR.

Jurisdictions are not required to adopt the recommendations of these bodies. As a result, the committee was told, there is some inconsistency with respect to drug coverage across the country. Additionally, some CADTH assessments are carried out at the request of a single jurisdiction, hospital or health authority, which can potentially add to the inequality of access through differences in formulary listings or inconsistencies in prescribing guidelines. This situation was noted particularly in the case of rare diseases, as described above under “Drugs for Rare Diseases,” in which off-label prescribing is prevalent.





ENHANCING SAFETY AND EFFECTIVENESS OF OFF-LABEL DRUG USE – A RENEWED CALL FOR FEDERAL LEADERSHIP AND TRANSPARENCY

Health Canada considers off-label drug prescribing to be a practice of medicine issue and emphasizes that its mandate does not include oversight of these individual patient-related medical decisions. However, Health Canada is responsible for the post-approval monitoring of prescription medicines, and this responsibility does not distinguish between drugs used for on or off-label purposes. Witnesses identified a number of approaches that could be implemented within the current infrastructure and in conjunction with recommendations made by this committee in the Clinical Trials Report and the Post-Approval Monitoring Report to enhance the safety and effectiveness of off-label drug use.

OPTIMIZE THE USE OF ALL ELECTRONIC FORMATS

In its Post-Approval Monitoring Report, this committee recommended that the Minister of Health discuss, with provincial/territorial counterparts, implementation of electronic systems to capture data related to prescription drugs. It further recommended the implementation of electronic medical records (EMRs) and electronic health records (EHRs) that are linkable to and compatible with those systems.

During the current study, the committee heard that other countries, including Israel and the United Kingdom, have succeeded in providing 100% of their citizens EMRs and EHRs. Within Canada, the committee was told about a research program at

McGill University using the Medical Office of the 21st Century (MOXXI), which involves a prototype EHR Network for urban, primary care providers in Quebec. The system includes an electronic prescribing component with a mandatory drop down menu of conditions, including off-label ones, for which a drug is being prescribed. In this way investigators were able to cross-reference drugs with Health Canada's drug product database to collect data on off-label prescribing. Such a system could be made available online to all physicians and could be expanded to require that the patient's age, pregnancy or nursing status be provided in order to identify vulnerable sub-groups of the population. The ability to gather and analyse data in this way was described as providing the capacity now to create international cohorts of people to allow worldwide monitoring of risks and benefits of on and off-label drug use. In addition, the committee notes that electronic prescribing could alert physicians when prescriptions are for an off-label indication or population sub-group. In this way, the system would help physicians become aware of off-label uses and provide the information to their patients.

The committee would like to reiterate the recommendation made in the Post-Approval Monitoring Report that electronic access to Health Canada's ADR reporting form should be made available to health professionals through EMRs and EHRs. However, consumer access to ADR report forms should also be facilitated.



As such this committee also recommended in the earlier report that Patient Information Leaflets accompany all prescription drugs when dispensed to consumers and that the leaflets provide information about reporting ADRs including Health Canada's website and phone number. While the committee commends the department for allowing electronic submission of ADR reports as well as mailed and faxed copies, it notes that navigating from Health Canada's homepage to the online reporting form is lengthy and not intuitive for those individuals unfamiliar with the site.

The committee therefore recommends that the Minister of Health, in conjunction with the recommendations 9, 10 and 11 in the committee's Post-Approval Monitoring Report regarding the implementation of electronic medical records, electronic health records and the electronic system of dispensed prescription drugs, urge the provinces and territories to:

- implement electronic prescribing and,
- require that prescriptions include information about indication and patient age, pregnancy or nursing status.

[recommendation 1]

The committee further recommends that the Minister of Health, at the next meeting of Canada's federal, provincial and territorial Ministers of Health, urge all jurisdictions to discuss mechanisms by which health professionals can inform patients of off-label prescription drug use, including disclosure of the information by the prescribing physician or the dispensing pharmacist. [recommendation 2]

The committee further recommends that the Minister of Health direct Health Canada to facilitate access to its online adverse drug reaction reporting form by:

- providing a direct link on the department's homepage; and,
- including this link, along with a direct telephone number for reporting adverse drug reactions to Health Canada, in the Patient Information Pamphlets, recommended in the report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness* that pharmacists must provide to patients with each prescription.

[recommendation 3]



COLLECT DATA ON OFF-LABEL PRESCRIBING

There is no formal mechanism in Canada to collect information about off-label drug prescribing or use. The committee was told that South Africa is able to collect that data by requiring prescribers to provide information about the indication for which the drug is being prescribed. It also heard about a new system in France whereby newly approved drugs can be granted Temporary Recommendations for Use (TRUs). The TRUs can be granted for a maximum of three years during which time the drug that has been approved for use for a given indication can be used off-label for stated indications although the drug maker must adhere to certain restrictions, the use must be monitored and the data collected. The TRU system has not been in place long enough to assess whether it is successful. As noted earlier in this report, off-label prescribing is more common for older drugs. As such, a system of following the off-label use of new drugs may not capture a significant proportion of off-label use.

The committee was told that all provinces and territories collect administrative information that could be used to track off-label drug prescribing. Currently, however, only Quebec requires that prescribers specify when their prescriptions are for off-label indications. The committee agrees with witnesses who argued that it is in the best interest of the provinces and territories to collect this information so that an evidence base can be established regarding the safety and effectiveness of drugs when used off-label. Such information can lead directly to cost saving in healthcare delivery, through reduced use of drugs that show little effectiveness and increased use of less expensive drugs that are shown to be effective.

Finally, the committee is concerned that a greater proportion of ADRs may be associated with off-label than on-label drug use. Health Canada

receives and assesses ADR reports that do not distinguish between the two uses. The committee agrees with those witnesses who stated that ADR reports should provide sufficient information to determine off-label use so that this safety issue can be examined. The committee's earlier study of the post-approval monitoring of prescription drugs revealed that Health Canada may submit a study request to DSEN based on its assessment of ADRs for a specific drug. Collecting information regarding the relationship between ADRs and on or off-label use of the drug could have a significant impact on the nature of the study that DSEN implements. Finally, the quality and quantity of ADR reports submitted to Health Canada affects the department's ability to detect safety signals. This committee proposed a number of actions in its Post-Approval Monitoring Report to encourage and facilitate ADR reporting both by patients and health professionals.

The committee therefore recommends that the Minister of Health direct Health Canada, in collaboration with its provincial and territorial counterparts, to identify common off-label uses of medicines using recent studies and available data on dispensed prescription drugs. [recommendation 4]

The committee further recommends that Health Canada's Adverse Drug Reaction report forms require the indication for use and other information necessary to determine off-label use be provided. [recommendation 5]



FACILITATE RESEARCH AND INFORMATION SHARING

The committee is confident that safety and effectiveness research of off-label drug use can be adequately addressed within the current infrastructure. Alain Beaudet, President of CIHR, stated that it has provided \$7.9 million over the past five years for research related to off-label drug use, including the recent study from McGill University that was frequently cited during this study.¹⁶

CIHR's Strategy for Patient-Oriented Research (SPOR), which aims to increase Canada's capacity for clinical trials, was also described. Beyond traditional clinical trials, the committee was told about CIHR's DSEN, which responds to queries from regulators, managers of publicly funded provincial and territorial drug plans, policy makers and technology assessors in order to increase the evidence base on matters related to drug safety and effectiveness, including evaluation in special or understudied populations. Robert Peterson, Executive Director of DSEN, asserted that the research methodologies used by DSEN, together with its commitment to global collaboration, are well suited to address issues of safety and effectiveness, including comparative effectiveness, for all prescription drug use, both on and off-label.

The committee would like to see improved information sharing among agencies and jurisdictions with respect to off-label drug use. Improved information sharing could contribute to greater efficiencies and reduced cost to the healthcare system. As such, the committee agrees with witnesses who suggested that there is likely to be good cooperation among jurisdictions to share information. CADTH's mandate is to provide analysis and recommendations to decision-makers in order to optimize the sustainability of the health system through policies that ensure the best value for money. Brian O'Rourke, President of CADTH, described the agency's work, which includes recommendations for formulary listing, therapeutic reviews and optimal use projects at the request of a

jurisdiction, health authority or health facility. The committee supports this work, however it would like assurances that the information that is generated through these exercises and that is relevant to the health systems of all jurisdictions is actively shared in order to optimize efficiencies. Health Canada is represented on the Board of Directors of CADTH and could play a role in enhancing the information-sharing capacity of CADTH.

Several witnesses referred to the need for an authoritative source of information for off-label uses of approved drugs. With respect to oncology drugs, the committee heard that the European Society of Medical Oncologists has called on regulatory authorities to create a compendium of cancer drugs and their associated acceptable indications, including some off-label indications. The committee supports the idea of a source of comprehensive comparative effectiveness information such as the *Australian Medicines Handbook* and the *British National Formulary* that is readily available to health professionals. While it would like to see a "made in Canada" version of these documents, it considers such an initiative to be one best discussed among national health professional organizations.

The committee therefore recommends that Health Canada convey information about common off-label drug practices that lack strong scientific evidence identified in Recommendation 4 to the Canadian Institutes of Health Research's Drug Safety and Effectiveness Network and request that it undertake to study these off-label uses in the most appropriate format including comparative effectiveness research. [recommendation 6]

¹⁶ T. Egualé, 2012



The committee further recommends that the Canadian Agency for Drugs and Technologies in Health ensure that when it responds to a request from one jurisdiction with information that could benefit the publicly funded health system of other jurisdictions that it take measures, wherever possible, to share the information across jurisdictions. [recommendation 7]

The committee further recommends that the Minister of Health look into mechanisms for making information sources such as the *Australian Medicines Handbook* and the *British National Formulary* available to Canadian health professionals. [recommendation 8]

ADDRESS OFF-LABEL USE IN VULNERABLE SUB-GROUPS OF THE POPULATION

The concerns raised with regard to vulnerable sub-groups of the population were similar to those raised during the committee's previous two studies on pharmaceuticals. In response to those concerns this committee recommended in its Clinical Trials Report that approval of new drugs should be dependent upon clinical trials having been performed in the same population that is reasonably expected to consume the drug once it is on the market. It also recommended in the

Post-Approval Monitoring Study that Health Canada have the authority, under updated legislation, to require drug manufacturers to conduct post-approval studies; that DSEN implement a strategy to conduct studies in sub-groups of the population; and that systematic safety reviews of drugs used in the pediatric population be implemented.¹⁷ Implementation of these recommendations would put into place the carrot and stick approach which the committee was told is necessary in order to improve clinical trial activity, not only in the pediatric population, but other vulnerable sub-groups of the population. This committee has also recommended in its previous reports on pharmaceuticals that DSEN make use of research networks to increase participation of vulnerable sub-groups. For example, the Mother, Infant, Child and Youth Research Network could be engaged to facilitate patient recruitment and study design.

The committee therefore recommends that the federal government implement recommendation 6 of the committee's report entitled *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* and recommendations 1, 3 and 12 of the committee's report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*, which address the need for more drug research in vulnerable sub-groups of the population and would provide the Minister of Health with the authority to require additional post-approval studies. [recommendation 9]

¹⁷ The committee acknowledges that since the drafting of this report, the Government tabled Bill C-17, an Act to amend the Food and Drugs Act. The bill proposes to update the legislation as recommended by this committee.



Off-label prescription drug use in the pediatric population is a particular concern. The committee agrees with the observation it heard that the stakes are higher when considering the children and youth of Canada and that ADRs in this population cannot always be extrapolated from the adult population. It is particularly concerned about the drastic increase in the off-label use of antidepressant and antipsychotic drugs in children. The committee notes the June 2013 article in the *Canadian Journal of Psychiatry* which described a drastic increase in the number prescriptions for antipsychotic drugs for children and it urged caution in their use.¹⁸ The use of antipsychotics and antidepressants among children and youth must be monitored closely. The committee applauds the efforts of the Canadian Paediatric Surveillance Program but would like to see focussed monitoring of these medicines in particular among children and youth. Similarly, the committee is concerned about the widespread use of antipsychotics among the elderly, particularly those in long term care facilities.

The committee therefore recommends that the Minister of Health direct Health Canada to explore ways to provide focussed and thorough monitoring of the off-label use of prescription drugs among children and youth less than 18 years of age, particularly the use of antipsychotics and antidepressants, including further collaboration with the Canadian Paediatric Society to enhance the Canadian Paediatric Surveillance Program and it would like to see focussed monitoring of the prescribing practices among the elderly by the appropriate authorities. [recommendation 10]

The committee further recommends that the Minister of Health work with provincial and territorial counterparts to encourage the implementation of effective monitoring of antipsychotic medication prescribing within long-term care settings in their respective jurisdictions and to update prescribing guidelines in this regard. [recommendation 11]

IMPROVE ASSESSMENTS

With respect to comprehensive assessments of off-label drug use, several witnesses referred to a product offered by the United Kingdom's National Institute for Health and Care Excellence (NICE) called "Evidence summaries: unlicensed/off-label medicines." The summaries review the strengths and weaknesses of available evidence to inform treatment and funding decisions.

CADTH, which conducts its assessments using a range of evidence sources, sits on DSEN's Steering Committee and therefore should be aware of the research DSEN has underway. The increased data collection and expedited research recommended above, combined with CADTH's access to the *Cochrane Database of Systematic Reviews*, will enable the agency to conduct more assessments of the safety and effectiveness of off-label drug uses, similar to the NICE project. In turn, these assessments will help provincial and territorial governments make formulary decisions which should be consistent across jurisdictions. Similarly, CADTH's work can also contribute to revised prescribing guidelines through the professional medical bodies. In this way, off-label

¹⁸ Rebecca Ronsley et al., "A Population-Based Study of Antipsychotic Prescription Trends in Children and Adolescents in British Columbia, From 1996 to 2011," *Canadian Journal of Psychiatry*, June 2013, vol. 58, no. 6.



uses found to be effective can be encouraged while those determined to be ineffective will no longer be publicly funded or endorsed in prescribing guidelines.

The committee therefore recommends that Health Canada request that the Canadian Agency for Drugs and Technologies in Health regularly conduct assessments of off-label drug uses to facilitate increased uniformity of formulary listings and prescribing guidelines across jurisdictions. [recommendation 12]

EXPAND THE ORPHAN DRUG FRAMEWORK

The Committee is pleased that Health Canada intends to implement an Orphan Drug Regulatory Framework. The new framework will be designed to encourage research, development and approval of new drugs for rare disorders. Health Canada officials stated that the framework will create an official orphan drug designation. This designation would then allow drugs to be eligible for such considerations as the tailoring of clinical trial design, waiving the cost-recovery fee for drug approval, priority review for market authorization and appropriate post-approval monitoring.

While this proposed framework marks a significant advance for orphan drug regulation in Canada, the committee is concerned that the off-label drug use of older drugs to treat many rare diseases is not being appropriately monitored and their effectiveness is not being properly assessed. The committee would like to see uniform access

across Canada for effective off-label use of older drugs and elimination of costly or ineffective off-label use of older drugs. For those drugs found to be effective, the new indications should be added to drug labels. Information about ineffectiveness should be made available.

The committee therefore recommends that Health Canada include within its proposed Orphan Drug Framework elements that pertain to older drugs including the promotion of research into the effectiveness of off-label uses and making the results of that research publicly available.

[recommendation 13]

ADDITIONAL OBSERVATIONS

The committee agrees that off-label drug prescribing involves the practice of medicine and the practice of pharmacy which are provincially and territorially regulated. However, these prescription medicines are federally regulated and there are additional concerns raised during this study that can be addressed by Health Canada. Implementation of the recommendations in this report will result in increased research and publicly available information regarding the safety and effectiveness of approved drugs, such as the indications for which or the population for whom the drug should be prescribed, beyond those that may be laid out in the product monographs of certain prescription drugs. The committee would like Health Canada, which is represented on the Board of Directors of CADTH and the Steering Committee of DSEN, to require changes to drug labels once these issues have been assessed by these bodies. In this regard,



this committee recommended in its Post-Approval Monitoring Report that the Minister should have the authority to require label changes.¹⁹ The committee further suggests that this authority could be used to make label changes that have been implemented in other jurisdictions with which Health Canada collaborates in terms of mutual recognition agreements.

The committee therefore recommends that Health Canada implement recommendation 1 of the committee's report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*, in order to exercise its authority to require label changes that reflect safety and effectiveness research on off-label drug use. [recommendation 14]

The committee further recommends that Health Canada ensure that label changes are accurately and automatically reflected in the Patient Information Leaflets recommended in the committee's report *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*. [recommendation 15]

The committee is concerned that Health Canada has not taken sufficient steps to address transparency issues in terms of the negative decisions it takes when assessing drugs for

approval. It is pleased that the department is taking steps in response to concerns raised in the November 2011 report of the Auditor General. The Auditor General recommended at that time that "Health Canada should disclose information related to new drug approvals in a timely manner and improve the transparency of 'approvals with conditions,' rejections, and withdrawals of new drugs so that Canadians and health care professionals can access information about these drugs."²⁰ Health Canada has indicated that it has complied with this recommendation and that it now provides this information in the Summary Basis of Decision (SBD) documents which originally provided information only about approvals. However, the committee would like the information provided in the SBDs to be expanded further. Witnesses suggested the SBDs for approved products should provide specifics about rejections and withdrawals for additional indications or population groups made in the New Drug Submissions (NDS) for initial market approval. Additionally, SBDs should be made available when the makers of approved drugs submit requests for subsequent expansion of indications or population groups through Supplemental New Drug Submissions (SNDS). In this way, information will be publicly available for all negative decisions and drug sponsor withdrawals.

The committee therefore recommends that Health Canada broaden the scope of information provided through Summary Basis of Decision documents beyond newly approved drugs to new indications for old drugs and that these documents provide information about rejections as well as drug sponsor withdrawals. [recommendation 16]

¹⁹ The committee acknowledges that since the drafting of this report, the Government tabled Bill C-17, an Act to amend the Food and Drugs Act. The bill proposes to update the legislation as recommended by this committee.

²⁰ Office of the Auditor General of Canada, Chapter 4, "Regulating Pharmaceutical Drugs—Health Canada," 2011 Fall Report of the Auditor General of Canada, p18.



Finally, the committee noted its concern regarding the manner by which physicians acquire information about approved prescription drugs in its Post-Approval Monitoring Report. It would like to reiterate this concern following the testimony from some witnesses who stated that physicians report learning about off-label uses from pharmaceutical sales representatives; a practice that is prohibited under the *Food and Drugs Act*. Health Canada indicated that it receives few complaints in this regard however the committee questions whether it is realistic to expect complaints about this practice. It also notes the difficulty of following up on such complaints given jurisdictional limits and Health Canada's inability to monitor the activities between physicians and drug sales representatives. Witnesses expressed frustration during this study that the current prohibition is essentially unenforceable. While the committee supports the intended goal of the prohibition, it agrees with those witnesses who questioned its practicality. The committee suggests that, in time, off-label prescribing will become limited to situations where the safety and effectiveness

of the drug's off-label use is not in question once Health Canada has implemented this committee's recommendations, not only those in this report but in the preceding two reports on prescription pharmaceuticals. In the meantime however the committee would like the issue of physician education of off-label drug use reiterated to each of the provinces and territories, which have jurisdiction in this regard.

The committee therefore recommends that the Minister of Health raise the concern about physician education related to off-label prescription drug use and the influence of drug sales representatives in this regard at the next meeting of Canada's federal, provincial and territorial Ministers of Health. [recommendation 17]

The committee further recommends that the Minister of Health direct Health Canada to examine the current prohibition on off-label drug promotion by drug manufacturers in order to identify effective mechanisms of enforcement. [recommendation 18]





CONCLUSION

In its third phase of the prescription pharmaceuticals study the committee has thoroughly examined the issue of off-label use, that is, the use of prescription drugs beyond the specifications set out in Health Canada's approval. Off-label prescribing and use of drugs is common and has often been associated with innovative new uses for existing approved medicines. However, because off-label uses pertain to indications, dosages or population sub-groups for which Health Canada did not assess clinical trial information, the safety and efficacy of these uses has not been established. Although it can be suggested that Health Canada's post-approval monitoring activities are designed to capture all prescription drug use, the committee urges the implementation of additional measures in order to further enhance the safety and effectiveness of prescription drugs for all Canadians, including those drugs used for off-label purposes.

Health Canada's approach to off-label prescribing of drugs has been that it is strictly a practice of medicine issue. However, this committee is concerned that prescribers as well as their patients frequently are not aware of when drugs are being used off-label and therefore that safety and effectiveness have not been thoroughly

addressed. This report makes a number of recommendations to address awareness in this regard but also to improve the collection and assessment of data on off-label drug use. Facilitating thorough assessments of off-label drug use, with particular emphasis on vulnerable sub-groups of the population, will in turn inform health care providers and drug plan managers of those uses that should be encouraged and those that should no longer be recommended. The committee is confident that implementation of the recommendations made in its first two reports on prescription pharmaceuticals will address many of the concerns that were raised with respect to the off-label use of prescription drugs. It emphasizes that optimizing the use of existing infrastructure and administrative data will also address some of the safety and effectiveness questions in this regard. In addition, however, this report's recommendations must be implemented in order to address critical information gaps. This comprehensive approach will optimize existing programs and resources, encourage further collaboration between jurisdictions and facilitate information sharing in order to obtain the most benefit while minimizing the risk to Canadians from off-label drug use.



APPENDIX A – LIST OF RECOMMENDATIONS

RECOMMENDATION 1

The committee therefore recommends that the Minister of Health, in conjunction with the recommendations 9, 10 and 11 in the committee's Post-Approval Monitoring Report regarding the implementation of electronic medical records, electronic health records and the electronic system of dispensed prescription drugs, urge the provinces and territories to:

- implement electronic prescribing and,
- require that prescriptions include information about indication and patient age, pregnancy or nursing status.

RECOMMENDATION 2

The committee further recommends that the Minister of Health, at the next meeting of Canada's federal, provincial and territorial Ministers of Health, urge all jurisdictions to discuss mechanisms by which health professionals can inform patients of off-label prescription drug use, including disclosure of the information by the prescribing physician or the dispensing pharmacist.

RECOMMENDATION 3

The committee further recommends that the Minister of Health direct Health Canada to facilitate access to its online adverse drug reaction reporting form by:

- providing a direct link on the department's homepage; and,
- including this link, along with a direct telephone number for reporting adverse drug reactions to Health Canada, in the Patient Information Pamphlets, recommended in the report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness* that pharmacists must provide to patients with each prescription.

RECOMMENDATION 4

The committee therefore recommends that the Minister of Health direct Health Canada, in collaboration with its provincial and territorial counterparts, to identify common off-label uses of medicines using recent studies and available data on dispensed prescription drugs.

RECOMMENDATION 5

The committee further recommends that Health Canada's Adverse Drug Reaction report forms require the indication for use and other information necessary to determine off-label use be provided.

RECOMMENDATION 6

The committee therefore recommends that Health Canada convey information about common off-label drug practices that lack strong scientific evidence identified in Recommendation 4 to the Canadian Institutes of Health Research's Drug Safety and Effectiveness Network and request that it undertake to study these off-label uses in the most appropriate format including comparative effectiveness research.

RECOMMENDATION 7

The committee further recommends that the Canadian Agency for Drugs and Technologies in Health ensure that when it responds to a request from one jurisdiction with information that could benefit the publicly funded health system of other jurisdictions that it take measures, wherever possible, to share the information across jurisdictions.

RECOMMENDATION 8

The committee further recommends that the Minister of Health look into mechanisms for making information sources such as the *Australian Medicines Handbook* and the *British National Formulary* available to Canadian health professionals.



RECOMMENDATION 9

The committee therefore recommends that the federal government implement recommendation 6 of the committee's report entitled *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* and recommendations 1, 3 and 12 of the committee's report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*, which address the need for more drug research in vulnerable sub-groups of the population and would provide the Minister of Health with the authority to require additional post-approval studies.

RECOMMENDATION 10

The committee therefore recommends that the Minister of Health direct Health Canada to explore ways to provide focussed and thorough monitoring of the off-label use of prescription drugs among children and youth less than 18 years of age, particularly the use of antipsychotics and antidepressants, including further collaboration with the Canadian Paediatric Society to enhance the Canadian Paediatric Surveillance Program and it would like to see focussed monitoring of the prescribing practices among the elderly by the appropriate authorities.

RECOMMENDATION 11

The committee therefore recommends that the Minister of Health work with provincial and territorial counterparts to encourage the implementation of effective monitoring of antipsychotic medication prescribing within long-term care settings in their respective jurisdictions and to update prescribing guidelines in this regard.

RECOMMENDATION 12

The committee therefore recommends that Health Canada request that the Canadian Agency for Drugs and Technologies in Health regularly conduct assessments of off-label drug uses to facilitate increased uniformity of formulary listings and prescribing guidelines across jurisdictions.

RECOMMENDATION 13

The committee therefore recommends that Health Canada include within its proposed Orphan Drug Framework elements that pertain to older drugs including the promotion of research into the effectiveness of off-label uses and making the results of that research publicly available.

RECOMMENDATION 14

The committee therefore recommends that Health Canada implement recommendation 1 of the committee's report entitled *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*, in order to exercise its authority to require label changes that reflect safety and effectiveness research on off-label drug use.

RECOMMENDATION 15

The committee further recommends that Health Canada ensure that label changes are accurately and automatically reflected in the Patient Information Leaflets recommended in the committee's report *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring for Safety and Effectiveness*.

RECOMMENDATION 16

The committee therefore recommends that Health Canada broaden the scope of information provided through Summary Basis of Decision documents beyond newly approved drugs to new indications for old drugs and that these documents provide information about rejections as well as drug sponsor withdrawals.



RECOMMENDATION 17

The committee therefore recommends that the Minister of Health raise the concern about physician education related to off-label prescription drug use and the influence of drug sales representatives in this regard at the next meeting of Canada's federal, provincial and territorial Ministers of Health.

RECOMMENDATION 18

The committee further recommends that the Minister of Health direct Health Canada to examine the current prohibition on off-label drug promotion by drug manufacturers in order to identify effective mechanisms of enforcement.



APPENDIX B – WITNESSES

Wednesday, February 27, 2013

Canadian Pharmacists Association	Dr. Jeff Poston, President
Canadian Psychiatric Association	Dr. Jitender Sareen, Chair, Research Committee
Canadian Association of Medical Oncologists	Dr. Kara Laing, President

Thursday, February 28, 2013

Canadian Paediatric Society	Dr. Anne Rowan-Legg, Member, Community Paediatrics Committee
The Society of Obstetricians and Gynaecologists of Canada	Dr. Jennifer Blake, Chief Executive Officer
Canadian Geriatrics Society	Dr. Allen Huang, Member

Wednesday, March 6, 2013

As Individual	Dr. Joel Lexchin , Professor, School of Health Policy and Management, York University
	Dr. Tewodros Eguale, Clinical and Health Informatics Research Group, McGill University Health Centre
	Robyn Tamblyn, Scientific Director, Research Institute, McGill University Health Centre

Thursday, March 7, 2013

Canadian Agency for Drugs and Technologies in Health	Dr. Brian O'Rourke, President and Chief Executive Officer
Institute for Clinical Evaluative Sciences	Dr. Paula Rochon, Senior Scientist
As an individual	Dr. Stuart MacLeod, Professor, Child and Family Research Institute, University of British Columbia

Wednesday, March 20, 2013

Rx&D	Walter Robinson, Vice President, Government Relations
	Jared Rhines, Scientific and Regulatory Affairs
BIOTECanada	Andrew Casey, President and Chief Executive Officer
Canadian Generic Pharmaceutical Association	David Windross, Vice-President of External Relations, Teva Canada



Thursday, March 21, 2013

Psychiatric Medication Awareness Group Janet Currie, Representative

Canadian Organization for Rare Disorders Maureen Smith, Secretary

Wednesday, April 17, 2013

Health Canada Dr. Marc Berthiaume, Director, Marketed
Pharmaceuticals and Medical Devices Bureau
(HPFB)

Dr. Supriya Sharma, Senior Medical Advisor,
Health Products and Food Branch

Canadian Institutes of Health Research Dr. Alain Beaudet, President

Dr. Robert Peterson, Executive Director, Drug
Safety and Effectiveness Network





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