KEEPING AN EYE ON PRESCRIPTION DRUGS, KEEPING CANADIANS SAFE

Active Monitoring Systems for Drug Safety and Effectiveness in Canada and Internationally

A COMMISSIONED DISCUSSION PAPER

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Health Council of Canada | Conseil canadien de la santé

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LIST OF ACRONYMS

ADR: Adverse drug reaction
AFSSaPS: Agence Française de Sécurité Sanitaire des Produits de Santé (France)
AHRQ: Agency for Healthcare Research and Quality (US)
BGTD: Biologics and Genetic Therapies Directorate
CDR: Common Drug Review
CERTs: Centers for Education & Research on Therapeutics (US)
CHMP: Committee for Medicinal Products for Human Use (European Medicines Agency)
CIHR: Canadian Institutes for Health Research
DEcIDE: Developing Evidence to Inform Decisions about Effectiveness (US)
DSEN: Drug Safety and Effectiveness Network (Canada)
DSRU: Drug Safety Research Unit (UK)
EAC: Expert Advisory Committee (Canada)
EAG: Expert Advisory Group (UK)
EMA: European Medicines Agency (European Union)
ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EU)
EPC: Evidence-based Practice Centers (US)
FDA: Food and Drug Administration (US)
FDAAA: Food and Drug Administration Amendments Act (US)
GAO: Government Accountability Office (US)
GPRD: General Practice Research Database (UK)
ISMP: Institute for Safe Medication Practices Canada
Medsafe: Medicines and Medical Devices Safety Authority (New Zealand)
MHPD: Marketed Health Products Directorate (Canada)
MHRA: Medicines and Healthcare products Regulatory Agency (UK)
NAS: New Active Substance
NICE: National Institute for Health and Clinical Excellence (UK)
NOC/c: Notice of Compliance with conditions (Canada)
OECD: Organisation for Economic Co-operation and Development
OSE: Office of Surveillance and Epidemiology (US FDA)
PDUFA: Prescription Drug User Fee Act (US)
PMPRB: Patented Medicine Prices Review Board (Canada)
REMS: Risk Evaluation and Mitigation Strategies
TPD: Therapeutic Products Directorate (Canada)
VA: Department of Veterans Affairs (US)
VRMM: Vigilance and Risk Management of Medicines (UK)

FOREWORD

While prescription drugs offer significant health benefits, the risks associated with their "real world" use remain largely unknown even after they become available for public consumption. In Canada and internationally, there is a growing recognition of the need for improved surveillance of drugs after they enter the market *(pharmacovigilance)*, yet developing such a system is a complex and challenging process.

The Health Council of Canada commissioned this independent discussion paper with two aims in mind: to raise awareness among Canadians about issues related to monitoring drug safety and effectiveness, and to stimulate productive dialogue about steps that can be taken to build an effective Canadian system of pharmacovigilance. This paper follows our 2009 status report and commentary, *The National Pharmaceuticals Strategy: A Prescription Unfilled*, in which we called for proactive strategies in Canada in several areas to ensure the safety of all those taking medications.

The goal of improving pharmacovigilance has been repeatedly endorsed by Canadian leaders. The *2003 First Ministers' Accord on Health Care Renewal* made it a priority to further collaborate to "ensure that drugs are safe, effective and accessible in a timely and cost-effective fashion." As part of the 2004 *10-Year Plan to Strengthen Health Care*, first ministers directed health ministers to establish a ministerial task force to develop and implement the National Pharmaceuticals Strategy, which included action to "strengthen evaluation of real-world drug safety and effectiveness." More recently, the 2008 Parliamentary report *Post-Market Surveillance of Pharmaceuticals*, made 18 recommendations for improving the Canadian system.

This paper explains why drug safety and effectiveness matters to Canadians and compares post-market surveillance regimes in Canada and key Organisation for Economic Co-operation and Development (OECD) countries. It further identifies ten key characteristics of sound pharmacovigilance systems in the international community that are applicable to Canada.

Finally, this discussion paper identifies ways to increase capacity to undertake high-quality pharmacovigilance studies in the interest of patient safety. It also outlines ways to increase the evidence on drug safety and effectiveness that is available to Canadian regulators, policy-makers, health care providers, and patients. This information will be invaluable to doctors, pharmacists and other health professionals in prescribing the safest and most effective medications and providing better health care to Canadians.

John G. Abbott, CEO
Health Council of Canada

EXECUTIVE SUMMARY

In this paper, we assess Canada's current system of post-market surveillance and outline several recent initiatives in this country. We also examine in detail the approaches adopted in other jurisdictions that are taking steps to improve pharmacovigilance. Our examination of drug safety regimes in the European Union (EU), the United States (US), the United Kingdom (UK), New Zealand, and France identified important issues with respect to governance, funding, independence and research standards, transparency, data access and ownership, and public oversight that are relevant to Canada. A comparison of international approaches highlights the strengths and weaknesses of these strategies relative to our own situation. The key issues that need to be addressed to enhance public safety and confidence in pharmaceuticals in Canada are discussed.

Drug Safety in Canada

Pharmaceuticals offer significant health benefits, but the risks associated with their use in the real world remain largely unknown when they enter the market and large numbers of people start taking them. This can leave users of medicines exposed to unanticipated drug effects. Periodically, the public's attention is drawn to drug safety issues by events such as the high-profile 2004 withdrawal of the anti-inflammatory and painkiller, rofecoxib (Vioxx™), from the Canadian market and media coverage of inquests into deaths associated with prescription drug use.

In general, however, most Canadians are not aware of the limitations inherent in pre-market testing of prescription drugs, nor do they realize that there is no systematic scrutiny of people's experiences with drugs after they have been approved and are available for sale. Drugs are approved based on company-sponsored clinical trials in which typically only a limited number of selected people take the drug over a relatively short period. The market for a drug tends to include a wider range of patients, many of whom have multiple medical conditions and may take a variety of medications for a prolonged period. In fact, an increasing number of people are exposed to unsafe drugs. For example, two of the five most heavily promoted drugs in Canada in 2000 and ones that were widely prescribed (Baycol™ and Vioxx™) were subsequently withdrawn from the market for safety reasons.

Health Canada, like regulators in many other countries, continues to rely primarily on voluntary reports of adverse drug reactions in order to detect safety problems with drugs once they have been approved for marketing. However, research shows that this passive system captures only between 1% and 10% of such adverse reactions. The inadequacy of this passive approach and mounting international concerns about post-market drug safety have prompted many countries to set up regimes to more actively track the use of pharmaceuticals after they have been approved for market. The aim is to protect the public through the early detection of emerging safety signals—indications that there might be safety concerns about a drug. This approach, called *pharmacovigilance*, is a systematic method of monitoring drug safety once the product is released onto the market. Pharmacovigilance is relatively new worldwide, is still evolving, and presents scientific and practical challenges. The toolbox to improve post-market prescription drug safety includes issuing conditional drug approvals, actively scrutinizing drug and health care databases for signals that a problem exists, requiring risk management plans and post-market research trials, and creating disease registries.

Challenges to Monitoring Drug Safety

Our national regulator, Health Canada, faces a number of challenges in dealing with drug safety. Under the *Food and Drugs Act*, Health Canada has limited authority to deal with post-market safety issues. It cannot require

companies to conduct post-market studies that track people's real world experiences taking a drug. It cannot compel companies to make labelling changes if a safety issue arises after a drug has been approved for marketing, and it does not have the power to independently monitor drug company patient registries. Health Canada has the authority to order a drug withdrawn from the market, but this power has rarely been exercised. The rofecoxib (Vioxx™) market withdrawal, for example, was voluntary on the part of the manufacturer.

When Health Canada does identify a safety problem, the effectiveness of its current forms of risk communication may be marginal at best. For example, in the period from 2002 to 2005, health professionals were sent three letters warning of serious adverse reactions associated with the use of two atypical antipsychotics in elderly patients with dementia. However, an analysis of prescriptions filled under Ontario's drug benefit program for senior citizens showed that the number of prescriptions for the drugs did not decrease, but instead increased in the period after the warning letter was issued. More effective ways of communicating safety messages are essential.

In April 2008, the federal government introduced legislation with an aim to move the drug regulatory system from an "all or none situation"—either license the drug or don't—to a position where the risks and benefits of drugs are continuously assessed throughout their lifecycle. The promise of this new system, called *progressive licensing*, is that ongoing re-evaluation of the risks and benefits of medications will pick up serious safety issues earlier and help to better target drug therapy. The legislation would have given Health Canada the authority to issue the market authorization for a drug subject to additional terms and conditions, and to suspend the authorization if the company did not follow through on its obligations. Although the legislation (Bill C-51) was ultimately withdrawn, Health Canada still appears to be committed to a system of progressive licensing.

In the absence of a coordinated national system of post-market surveillance in Canada, local research institutes have engaged in post-market research projects. Additionally, partnerships among industry, academics, and individual provinces have initiated pharmacoviligance programs for specific drugs or diseases. For example, the province of Alberta has a program to monitor biologic agents used in the treatment of rheumatologic diseases, and the Pharmaceutical Outcomes and Policy Innovations Programme at the Children's and Women's Health Centre in British Columbia has several projects to inform the drug regulatory process and improve the safe use of drugs given to children.

As well, several Canadian academic/research units provide post-market surveillance expertise to provincial drug plans on a contract basis or with year-to-year funding. Some, like the Institute for Clinical Evaluative Sciences in Toronto, the Population Health Research Unit at Dalhousie University, and the Manitoba Centre for Health Policy at the University of Manitoba, have researchers who focus on prescription drug issues within a larger research unit. At the units, some studies are funded by peer-reviewed grants and some are funded directly by provincial drug plans.

A Pharmacovigilance Network for Canada

A June 2008 parliamentary report, *Post-Market Surveillance of Pharmaceuticals,* had recommended that a drug safety and effectiveness network be established "immediately." As a result, in 2009, the federal government took a significant step towards coordinating research into post-market drug safety when it announced ongoing funding for the Drug Safety and Effectiveness Network (DSEN), which is sponsored under the granting authority of the Canadian Institutes for Health Research. The DSEN, a virtual network, is designed to connect researchers throughout Canada together to conduct post-market drug research that is independent of pharmaceutical companies and to stimulate research to study the impact of drugs as they are used by Canadians. Similar research networks already exist in the United States and are being developed in the European Union.

Implications for Canada

The key issues around drug safety and effectiveness are explained and given a Canadian context in this paper so that drug companies, researchers and governments can consider improvements to make our system more effective. A summary of the key conclusions follows:

- It is important that Canadian academic centres commissioned to conduct post-market epidemiological studies on drug safety and effectiveness have access to the data from both public and private drug benefit plan prescription drug records and health care records, disease registries, the Common Drug Review (CDR), the Patented Medicine Prices Review Board (PMPRB), and other public and private organizations.
- Adequate and ongoing public funding is needed to: enable safety (pharmacovigilance) and effectiveness research that is free of bias and conflicts of interest, ensure open access to research data, increase transparency, and avoid the problems associated with industry nondisclosure of unfavourable findings.
- Until a sufficient pool of expertise is developed in Canada, it appears that the emerging DSEN will require ongoing support from the Canadian Institutes for Health Research, the Social Sciences and Humanities Research Council, and the Natural Sciences and Engineering Research Council to stimulate the development of new research methodologies and to increase research capacity.
- All post-market research that Health Canada requires from companies, or that is publicly commissioned, should be registered prior to commencement, avoid conflict of interest, and be subject to guidance documents to ensure a rigorous methodology is followed.
- Broad stakeholder involvement should be strongly encouraged in decision-making concerning publicly commissioned post-market studies.
- All members on any committees set up by Health Canada to deal with drug safety issues should submit conflict of interest disclosures to which the public has access. Avoidance of conflict of interest, whenever possible, should be the ultimate objective.
- It is strongly advised that Health Canada adopt a protocol for developing drug safety messages to be sent to provinces and territories, and other government agencies, health care practitioners and consumers, along with methods to monitor and evaluate the effectiveness of the messages.
- Health Canada should institute a mechanism to monitor and evaluate the effectiveness of Canadian initiatives to identify and respond to drug safety issues.
- It is vital that Health Canada be given the legislative authority to impose penalties for failure to complete post-market safety studies by the required deadlines. Other options, such as a temporary ban on promotion, or a temporary suspension of marketing authority, could be considered in order to ensure that Health Canada can enforce its requirements for post-market studies.
- Health Canada should make public all post-market commitments that it requires from industry along with annual reports regarding the progress of these commitments.

The recommendations above, including some specific suggestions for enhancing the DSEN, are elaborated on in the *Issues and Implications for Canada* section of this paper.

It is our hope that this paper, by providing insights and lessons based on international experiences, will help point the way for Canada to develop more responsive systems of research, regulation, and risk warning that lead to safer and more effective use of medications, advance the health of the population, and help to sustain our health care system.

INTRODUCTION

The Health Council of Canada commissioned this paper to inform Canadians and stakeholders about drug safety and effectiveness issues in Canada and abroad, and about the critical role that pharmacovigilance plays in ensuring the safe and effective use of drugs.

Through critical analysis and assessment processes, this paper presents a synthesis of what Canada is doing well, what we need to improve, what is happening globally, and what different jurisdictions can learn from one another. The objective is to outline ways that we (Canadians) can improve our knowledge and work processes, and what we should consider doing differently in order to achieve the following two objectives: (1) to increase the available evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers, and patients; and (2) to increase capacity within Canada to undertake high-quality post-market drug safety and effectiveness research. These objectives also form the basis for activities of the Drug Safety and Effectiveness Network (DSEN), announced in 2008 and sponsored under the granting authority of the Canadian Institutes for Health Research. The specific aims of this discussion paper are to:

a) address why drug safety and effectiveness matters, and should matter, to Canadians;
b) provide a comparative analysis of drug safety and effectiveness regimes in Canada and key countries in the Organisation for Economic Co-operation and Development (OECD);
c) analyze the issues at play and related developments within key international jurisdictions, as well as in Canada, to help inform Canadians and stakeholders about this very important pharmaceuticals management issue; and
d) offer valuable data sources, up-to-date information, and context on the approaches that Health Canada should take to pharmacovigilance based on the experiences of other countries.

This paper summarizes the Canadian and international contexts and recent initiatives. The first section addresses the reasons why the safety and effectiveness of medicines is an important issue. The Canadian system for post-market surveillance is described, including Health Canada's current authority as well as recent provincial and federal initiatives. International approaches to pharmacovigilance are outlined in *Section 2* where the strengths and weaknesses of these international strategies are highlighted using an analytic framework. *Section 3* emphasizes the key issues that need to be addressed to enhance public safety and confidence in pharmaceuticals in Canada.

Our method of analysis involves comparing and highlighting best practices regarding pharmacovigilance in order to address questions of safety and effectiveness of medicines. We examine systems in the European Union (EU) as well as the United States (US), the United Kingdom (UK), New Zealand, and France. The five international jurisdictions were selected because their relative similarity (as Western developed nations with well established regulatory frameworks) allows for generalizability, while at the same time they are sufficiently heterogeneous to cover a spectrum of approaches.

For this paper we drew on our previous work for the Canadian Patient Safety Institute (CPSI) and the Canadian Institutes of Health Research (CIHR).[1] We used information that we had previously gathered for these countries from both documentary analysis and interviews. Sources were the pharmacovigilance section of the EU's Committee for Medicinal Products for Human Use, the U.S. Department

of Veterans Affairs Center for Medication Safety, the U.S. Centers for Education and Research on Therapeutics, the UK Drug Safety Research Unit, UK Medicines and Healthcare Regulatory Agency, and in France, the Haute Autorité de Santé Commission de la Transparence, the Agence Française de Sécurité Sanitaire des Produits de Santé, the Surveillance du Risque, the Département du Bon Usage et de l'Information sur les Médicaments, a regional pharmacovigilance centre, and la Revue Prescrire. We updated that information with a fresh series of literature and government document reviews and semi-structured interviews with international key informants within the following: an international regulatory agency (the EU's European Medicines Agency, EMA), a national drug regulatory agency (the U.S. Food and Drug Administration, FDA), a drug surveillance system (the New Zealand Centre for Adverse Reactions Monitoring), a national health technology assessment agency (the UK's National Institute for Health and Clinical Excellence, NICE), a research network in the US that takes on task-order initiated projects from the FDA and the Agency for Healthcare Research and Quality (Developing Evidence to Inform Decisions about Effectiveness, DEcIDE), and the U.S. Department of Veterans Affairs (VA). In addition, we obtained written responses from, and interviews with officials in provincial and territorial drug plans (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Northwest Territories, and Yukon Territory) and from Health Canada. Key informants' consent was obtained to participate in an interview and to identify their organization. After the interview, key informants were asked to review the section of the report that incorporated information from their interview to confirm the accuracy of our interpretation of their quote(s) and the information they provided.

SECTION 1: PHARMACOVIGILANCE IN CANADA

(A) Post-Market Surveillance: Why it is an Important Topic for Canadians

Periodically, media coverage of the high-profile withdrawal of drugs from the Canadian market—such as the 2004 withdrawal of rofecoxib (Vioxx™)[a]—draws the public's attention to issues concerning the safety of drugs that are already on the market. In general, however, Canadians are not aware of the limitations inherent in pre-market testing of prescription drugs, nor do they realize there is no systematic scrutiny of what happens when large numbers of people start taking drugs that have been tested on only a limited number of people. This scrutiny, known as *post-market surveillance* or *pharmacovigilance*, involves protecting the public by monitoring drugs for both safety and effectiveness[b] after they have been approved and are on the market.

"*We do not actively really support or integrate post-market surveillance into health care,*" one provincial informant observed (Provincial Key Informant, March 2010). However, as Health Canada officials acknowledged in our correspondence with them, "*Health Canada lacks regulatory authority to act effectively in the post-market area.*"

Worldwide, attention is now being drawn to the need to better track patients' experiences with drugs in order to minimize any harmful effects. Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines after they are marketed, in order to identify new information about hazards associated with medicines and to prevent harm to patients. Currently pharmacovigilance is, as Health Canada noted in its correspondence with us, "*an evolving science in all jurisdictions.*" There are two key reasons why increased pharmacovigilance is important to Canadians: first, an increase in the number of people exposed to unsafe drugs and second, morbidity and mortality from prescription drugs.

1. Increase in the number of people exposed to unsafe drugs

Since the mid-1980s, between 3% and 4% of drugs approved in a five-year period in Canada have had to be withdrawn for safety reasons.[2] The percentage of drugs that is eventually withdrawn has not changed over the past 25 years. However the number of people exposed to unsafe drugs has been increasing.

> "*The average Joe Blow out there thinks when they start taking a drug,'Oh, it's been approved by Health Canada, it must be safe and effective.'* "
> (Provincial Key Informant, March 2010)

In the mid to late 1990s, 5.4 million people were exposed to bromfenac (Duract™), dexfenfluramine (Redux™), and mibefradil (Posicor™)[c] during the two to four years that those drugs were on the United States (US) market.[3] Two of the five most heavily promoted drugs in Canada in 2000, and ones that were widely prescribed—cerivastatin (Baycol™) (used to treat high cholesterol) and rofecoxib—were subsequently withdrawn because of safety issues. Between 1999 and September 2004, when rofecoxib was removed from the market, about 16 million Canadian prescriptions had already been written for it.[4]

There are three main reasons why new drugs are inherently less safe than older products: a) there is limited data when drugs are initially licensed, b) approval of new drugs is often based on surrogate endpoints[d] rather than a change in clinical condition, and c) some drugs are approved without complete data under expedited approval procedures.

[a] Here, and in the rest of this document, ™ is used to indicate the brand or trade name of a medication.

[b] *Effectiveness* is a term used to denote how well a drug works under real world circumstances. *Efficacy* is a term used to denote how well a drug works under the controlled circumstances of a clinical trial.

[c] Bromfenac was used for the treatment of pain, dexfenfluramine for appetite suppression and mibefradil for high blood pressure and coronary artery disease. Bromfenac and mibefradil were never approved in Canada.

[d] A *surrogate endpoint* is an intermediary measure that is used as a substitute indicator for a clinical endpoint (a change in clinical condition) . Examples of surrogate endpoints for specific diseases include: blood pressure or lipid levels for cardiovascular disease; blood glucose levels or HbA1c for diabetes, and tumour regression for cancer.

a) Limited data when drugs are initially licensed

More than $25 billion is spent annually on the purchase of prescription drugs in Canada,[5] and although pharmaceuticals are assessed for safety and efficacy before they are approved for marketing, this drug assessment/evaluation involves a risk:benefit analysis recognized as incomplete given the much larger post-market experience to follow.[1, 6-9] The market for a product once it has been approved most often includes patient and disease groups that were never assessed in pre-market clinical trials.[1, 7, 10]

> *"We're not going to find everything in a clinical trial. You're not going to have widespread use [as] in the population, you're not going to have as many people on different medications that could potentially interact with each other."* (Provincial Key Informant, February 2010)

Indeed, patients who have a condition in addition to the one the drug aims to treat (a concomitant disease) are frequently deemed ineligible to participate in pre-marketing clinical trials of that drug. As a result, at the time of market approval the effect of a newly approved drug on populations with multiple medical conditions is unknown, even though the risk for harmful drug interactions is often higher among those patients than among the people in whom the drug was tested in pre-marketing studies. Moreover, one key informant believed that study cohorts of women and children should be included in pre-marketing clinical trials. Currently, there is a guideline from Health Canada about the inclusion of women in clinical trials, but compliance is voluntary and cannot be enforced. Similarly, there is a non-enforceable guideline regarding the inclusion of children.

> *"The cohorts of people that are in the studies are very limited. I think what's required for licensing needs to be beefed up."* (Provincial Key Informant, March 2010)

Studies have established that pre-marketing clinical trials cannot detect rare events because the trials involve insufficient numbers of patients. As well, clinical trial duration is too brief to identify events that occur only after prolonged exposure to the medication.[6, 7, 11, 12]

> *"Some of the studies I've seen for chronic conditions are 12 weeks. I shake my head.… The amount of safety data you're going to collect in a 12–24 week trial is pretty minimal for the type of medication that's going to be chronic."* (Provincial Key Informant, March 2010)

> *"… it's not always the best thing to go for the drug that's the newest, latest, because you're technically an early-stage guinea pig."* (Provincial Key Informant, February 2010)

Given the lack of systematic prospective monitoring of drugs once they are marketed, signals for adverse drug reactions may remain undetected for prolonged periods, leaving users of medicines exposed to unanticipated drug effects. Drugs may be marketed for decades before serious adverse effects come to light (Table 1).

PRE- AND POST-MARKET PHASES OF DRUG TESTING

Drugs go through three phases of testing before they are marketed.

Phase I testing takes place in healthy volunteers to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

Phase II testing takes place in several hundred people and consists of controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition.

Phase III testing usually involves several hundred to several thousand patients and is intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit:risk relationship of the drug.

Post-market studies are referred to as Phase IV tests. Phase IV studies may be requested by regulatory authorities or may be undertaken by the sponsoring company to assess a drug's effectiveness for a new indication or for other reasons, such as testing for interactions with other drugs, or testing in certain population groups such as the elderly. They are designed to detect rare or long-term adverse effects in a larger patient population and over a longer time than was possible during the Phase I, II and III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being removed from the market, limited to certain populations or indications, or in the issuance of safety warnings. Currently, Health Canada has no authority to require companies to undertake Phase IV studies for approved drugs once they are available on the market.

b) Approval of drugs based on surrogate endpoints

Regulators may approve drugs based on the results of studies using surrogate endpoints. Health Canada permits surrogate endpoints to be substituted for a change in clinical condition (clinical endpoints) in both the expedited and the traditional approval processes. Some surrogate endpoints have been validated against hard clinical outcomes, e.g. the relationship of CD4 counts to mortality from HIV/AIDS, but numerous drugs approved on the basis of surrogate endpoints have been found to have serious safety issues. Even for diseases where patient health may not be affected for a considerable period of time, for example diabetes, regulatory agencies are now requiring clinical trials that show improvements in morbidity and mortality rather than just the ability of the medicine to lower blood sugar.[13] Pre-marketing drug studies that use surrogate endpoints may obscure the true impact of drugs studied because a beneficial change in the surrogate may not predict clinical benefit.[14] An example from several decades ago was the use of flecanide (Tambocor™) and encainide (Enkaid™) to treat cardiac arrhythmias in the expectation of reducing the number of sudden cardiac deaths. The drugs were approved based on surrogate markers. However, when tested in a randomized controlled trial these drugs actually increased mortality.[15] A much more recent example is the case of

TABLE 1: DRUGS WITHDRAWN FROM THE CANADIAN MARKET AUGUST 2004 TO DECEMBER 2009

Drug		Approval date/date of first listing in *Compendium of Pharmaceuticals and Specialties*	Withdrawal date	Reason for withdrawal
Generic name	**Brand name**			
aprotinin	Trasylol™	Oct 3, 1995	Nov 23, 2007	Increase in all-cause mortality
estradiol dienanthate / estradiol benzoate and testosterone enanthate	Climacteron™	1961	Oct 22, 2005	Endometrial hyperplasia/ carcinoma possible because appropriate progestin regimen unknown
gatifloxacin	Tequin™	Jan 9, 2001	Jun 29, 2006	Serious disorders of glucose metabolism (nothing posted on Health Canada website concerning withdrawal)
lumiracoxib	Prexige™	Nov 2, 2006	Oct 3, 2007	Risk of serious hepatotoxicity cannot be safely and effectively managed
pergolide	Permax™	1991	Aug 30, 2007	Valvulopathy (damage to heart valves)
rofecoxib	Vioxx™	Oct 25, 1999	Sept 30, 2004	Increased relative risk for confirmed cardiovascular events, such as heart attack and stroke
tegaserod	Zelnorm™	Mar 12, 2002	Mar 30, 2007	Increase in cardiovascular ischemic events
thioridazine	Mellaril™	1959	Sept 30, 2005	Cardiac dysrhythmias
valdecoxib	Bextra™	Dec 11, 2002	Apr 7, 2005	Life-threatening skin reactions

Source: Lexchin (2009)[2]

rosiglitazone (Avandia™), which was approved as an oral antihyperglycemic agent to treat Type II diabetes. A meta-analysis later found that it is associated with an increased risk of death from cardiovascular causes.[16]

In September 2010, the EMA withdrew Avandia™ from the European market due to the risks it poses, and the FDA introduced measures to limit its use through a restricted access program. As of October 2010, Health Canada had not yet addressed the growing concerns.

c) Expedited drugs approvals

Waiting for definitive proof of efficacy may delay the availability of new and potentially beneficial drugs that aim to treat serious and often fatal diseases such as HIV/AIDS and many forms of cancer for which treatment is inadequate. In an attempt to make these treatments available in a timely manner, in 1998 the Therapeutic Products Programme (now the Therapeutic Products Directorate, TPD) instituted a new policy, the Notice of Compliance with conditions (NOC/c). The goal of this policy was to "provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs" where surrogate markers suggested that these new products offered "effective treatment, prevention, or diagnosis of a disease or condition for which no drug is presently marketed in Canada or significantly improved efficacy or significantly diminished risk over existing therapies…"[e] In return, companies would have to commit in writing to undertake confirmatory clinical studies—studies that definitively establish efficacy—and submit the results of these to the TPD.[25] This policy was modified in 2006.[26] Between 1998 and July 2010, 52 new drugs or new indications for drugs were approved under a NOC/c without fulfilling their conditions. Twenty-one products (or indications) have fulfilled their conditions, four have had their conditions either suspended or revoked, and the remaining 27 are still being sold under a NOC/c.[27, 28] There has not been any formal evaluation of the value of the drugs approved under this policy.

Based on promising findings, the drug gefitinib (Iressa™) was approved under a NOC/c in late 2003 for the treatment of lung cancer. In early 2005, it was shown to be ineffective for this condition. Gefitinib did not show any overall survival benefit and therefore did not fulfil the conditions of its NOC/c. Instead of removing the drug from the market, Health Canada let it continue to be used and subsequently restricted it to a subgroup of patients who could potentially continue to benefit from the drug.[29]

> *"But at the end of the day—no matter how you slice it, unless you are willing to spend a lot of money and people resources in expanding the review process, it's going to be offset by increased risks to the public."*
> (Provincial Key Informant, February 2010)

Bevacizumab (Avastin™) is a drug that was approved by the U.S. Food and Drug Administration (FDA) in 2008 and Health Canada in 2009 to treat breast cancer, based on the surrogate endpoint of suppression of tumour growth. Subsequent studies showed that the drug did not improve overall survival. The U.S. Government Accountability Office (GAO) ruled that, whenever surrogate endpoints have been used to expedite the approval process, post-market studies are required to determine clinical benefit. In Canada, bevacizumab was approved under an NOC/c, and its manufacturer, Hoffmann-La Roche Ltd., is supposed to be carrying out additional clinical studies.[14, 30] However, the status of those studies is unknown because that information is treated as confidential by Health Canada.[31]

2. Morbidity and mortality from prescription drugs

In the US, adverse drug reactions (ADRs) are the fourth to sixth leading cause of death, contributing to more than 100,000 deaths and 1.5 million hospitalizations each year.[32] Since that estimate was made in the late 1990s, the severity of the problem has increased. Reported serious adverse drug events[f] increased 2.6-fold from 1998 to 2005 (34,966 to 89,842), and fatal adverse drug events increased 2.7-fold during the same period, from 5,519 to 15,107. During the same period, the total number of outpatient prescriptions written increased by only 40%.[33]

In the US, Graham and colleagues estimate that in the five years (1999–2004) that rofecoxib was on the market, there were between 88,000 and 140,000 "excess cases of serious coronary heart disease," with 44% of these people dying as a consequence of their heart problems.[34] Although these figures come from the US there is no reason to believe that the situation is any different in Canada.

Despite the importance of recognizing ADRs, it is generally agreed that the system for reporting them is inadequate. Signal detection—the ability to pick up on indications that

[e] About 5% of drugs are approved under a NOC/c. [17-24]

[f] An *adverse drug event* is anything that happens to a patient while taking the drug whether or not the event is specifically related to the medication. An *adverse drug reaction* is an event that is linked to the drug being used.

something unusual or harmful is happening—is hampered by the continued reliance on voluntary reporting of ADRs as the primary means of pharmacovigilance in Canada, the EU, the US, the UK, New Zealand and France.[g] Voluntary reporting of ADRs reportedly captures only 1–10% of all such reactions.[35-37]

> *"The thing that I think of when I think of post-marketing surveillance is mainly the adverse drug reaction reporting —which does not go so well. … There's no easy way to deal with signals of safety issues, other than through the ADR reporting, which is not very robust, because it's voluntary and people just don't use it."*
> (Provincial Key Informant, March, 2010)

Limitations inherent in systems for spontaneous reporting of ADRs include the following: (1) reporting rates are highest for newly marketed drugs and decline markedly over time,[6] (2) those who could report an adverse reaction fail to do so if they are unsure if the reaction is related to drug exposure or believe that the ADR is already well known,[38] and (3) reporting rates are influenced by media coverage; they increase when there is negative publicity.[6] For example, in the UK, reporting is highest within the first two years post-approval of new drugs, a period during which an inverted black triangle symbol is placed adjacent to the medicine's name in official compendiums and advertising.[39-41] After the black triangle is removed, only serious or previously unrecognized ADRs are typically reported.[40]

> *"I'm not sure that legislating reporting is the way to go, but I think [reporting] even smaller or less serious events and effects of medications should be encouraged."*
> (Provincial Key Informant, February 2010)

Moore and colleagues note that while the FDA in the US received an average of 82 reports about ADRs related to digoxin annually in the late 1980s, data-mining of Medicare records for the period 1985–1991 revealed that more than 200,000 hospitalizations were due to ADRs secondary to digoxin over a seven-year period.[42]

Although France has a mandatory reporting requirement, one French study estimated that as few as one in 24,000 reactions were reported to the Regional Pharmacovigilance Centre. Even for serious and previously unrecognized reactions, the estimate was one in 4,600.[43]

Another example of where ADR reporting failed to uncover serious safety issues involves the use of post-menopausal hormone replacement therapy (HRT) that has now been linked to increased cardiovascular events (strokes and heart attacks) and breast cancer. In the decades during which it was used to alleviate the symptoms of menopause, reduce cardiac events, and increase bone density, ADR reporting did not reveal the link between HRT use, cardiovascular events and breast cancer. Clarification of these effects required systematic analysis through a randomized controlled trial that specifically looked for these outcomes to establish a relationship.[44]

(B) The Current System of Post-Market Surveillance in Canada

As Health Canada noted in its response to our queries (March 18, 2010):

> *"…once a product reaches the market and new safety information becomes available about its use in the broader population, there are currently few regulatory obligations on the manufacturer to continue to produce or share this information with the government. Other than a requirement to report adverse drug reactions, the Canadian Government cannot compel a manufacturer to carry out post-market activities, including long-term post-market safety studies."*

The only limited exception to this situation is if Health Canada approves a drug under a NOC/c. In that case, heightened post-market safety monitoring may be imposed as part of the NOC/c—but even in this situation study completion does not appear to be monitored. Furthermore, Health Canada cannot issue a NOC/c solely on the grounds that there are unresolved safety concerns with the new product.[31]

Health Canada faces challenges in a number of areas including (1) limited resources to conduct post-market surveillance of prescription drugs (2) under-reporting of ADRs and (3) conditional approvals and patient registries.

1. Limited resources

Health Canada's Marketed Health Products Directorate (MHPD) was created in 2002 and is responsible for *"improving the collection, analysis and dissemination of post-market safety and effectiveness information."* (Health Canada correspondence, March 2010) However,

g Manufacturers are required to report ADRs in all countries studied. Reporting by health care providers, and patients where permitted, is voluntary in all countries except France where it is compulsory.

this directorate has considerably fewer resources than the two directorates that are responsible for approving prescription drugs and biologic and genetic therapies. Figures from Health Canada for 2004 show that, combined, the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) had over seven times the funding and number of employees as the MHPD[45, h] (Table 2). By 2010, the situation had changed, but the TPD and the BGTD, which together had approximately 827 staff (full-time equivalent) and a combined operating budget of $74.6 million, still had more than 3.8 times the MHPD's approximately 214 staff and more than three times its $23.6 million budget.[46]

In April 2010 the minister of health tabled for parliamentary review a User Fee Proposal for Health Canada's human drugs and medical devices programs. This proposal will allow Health Canada to collect increased fees from the pharmaceutical and medical device industries for performing certain activities. According to the document, the updated fees will provide stable funding for key regulatory activities, but there is nothing in the document about how the increased funding will be allocated between the drug approval process and post-market pharmacovigilance.[47]

TABLE 2: COMPARISON OF PERSONNEL AND RESOURCES OF HEALTH CANADA DIRECTORATES

	Annual operating cost base ($ 000,000)		Number of full-time equivalent employees	
	Year ending Mar 31, 2004	Year ending Mar 31, 2010	Year ending Mar 31, 2004	Year ending Mar 31, 2010
Therapeutic Products Directorate	38	44.9	423	514.5
Biologics and Genetic Therapies Directorate	22	29.7	228	312.2
Marketed Health Products Directorate	8	23.6	90	213.9
Total	**68**	**98.2**	**741**	**1040.6**

Source: Progestic International (2004)[45] and Health Canada (2010)[46]

2. Adverse drug reaction reporting

Through the MedEffect Canada portal, which was launched in 2005, consumers, patients and health providers can report adverse drug reactions and access information about the safety of drugs and other products. Adverse drug reactions are reported to the Canada Vigilance Database, which was formerly known as the Canadian Adverse Drug Reaction Monitoring Program. ADR reports from health care professionals, medicines users, and caregivers can be reported directly to the National Office of Canada Vigilance or to one of seven Canada Vigilance regional offices, which then forward reports to the National Office for assessment.[48]

> *"Compliance with it [ADR reporting] is not great."*
> (Provincial Key Informant, March 2010)

Canada was the first developed country to make ADR reports publicly available online, at the Canada Vigilance Adverse Reaction Online Database.[49] The searchable database is available at http://www.hc-sc.gc.ca/dhp-mps/medeff/ databasdon/index-eng.php. The database contains suspected ADRs for prescription and non-prescription drugs, natural health products, biologics and radiopharmaceuticals.[48]

In 2008, Health Canada received 16,272 unique domestic reports of suspected adverse reactions of which 11,596 concerned pharmaceuticals while the balance concerned biotechnology products (3,303), biologics (792), radiopharmaceuticals (292), and natural health products (289). Health Canada assessed nearly 70% of all the reported cases as serious.[50] Yet these numbers probably represent only a minority of the actual number of ADRs. According to one Health Canada research study, about 30% of health professionals stated that they had ever reported an ADR, although in the prior year only about 20% had filed a report.[38]

> *"How do we get patients involved in [ADR reporting]?… I don't think we can afford to do it through the ways we've done it. It will become linking of databases and capture of information that we then do a lot of data-dredging on."*
> (Provincial Key Informant, February 2010)

h The Therapeutic Products Directorate approves and monitors prescription and non-prescription drugs derived from chemical manufacturing and medical devices; the Biologics and Genetic Therapies Directorate is responsible for biological and radiopharmaceutical drugs including blood and blood products, viral and bacterial vaccines, genetic therapeutic products, tissues, organs and xenografts. The Marketed Health Products Directorate monitors the safety of medications (and other products) once they have been approved for marketing.

> "*… make it a requirement that within the first two years, or whatever period of time of a new medication, [companies] have to include an insert with the product to say 'This is a new medication, and if you experience any adverse effects, please report through MedEffect'… we said, instead of making everyone report, why don't you pick your larger centres or larger prescribing facilities and get them on board to agree to report everything, even minor.*" (Provincial Key Informant, February 2010)

Health Canada also collects information on ADRs that have been reported in other countries. In 2008, *market authorization holders*—the manufacturers of the regulated health products—reported 241,417 foreign adverse reactions to Health Canada.[50] In Health Canada's correspondence with us, it reported that it is implementing an initiative to access the ADR data from the US FDA and other regulatory agencies to facilitate in-depth safety data analysis and proactive risk management, but the extent of this initiative was not made clear.

Studies in various countries found a range of rates of under-reporting of ADRs. In some practice settings, although monitoring found that many ADRs occurred, it is estimated that as few as 6% of the ADRs were reported.[35]

3. Patient registries as requirements for conditional approval or market re-entry

The establishment of a patient registry[i] may be a condition for a drug to receive marketing approval or for a drug to re-enter the marketplace after having been withdrawn for safety concerns.[11] Examples of drugs that are only accessible through a drug registry program include clozapine (Clozaril™), a treatment for schizophrenia, and alosetron (Lotronex™), a treatment for irritable bowel disease in women. Patient registries facilitate the long-term monitoring of people with a particular condition in order to follow the course of the illness and the response and side effects from any treatment. Registries may also reduce the population exposed to high-risk drugs, allow for post-market studies, and provide earlier signals of safety issues than population-level analyses or clinical trials.[11] However, the financing of registries and how information in them can be accessed and used, can be controversial.

> "*I think one of the reasons that it [the clozapine registry] was successful is that it was company-based. So the company was required to put the resources into place.*" (Provincial Key Informant, February 2010)

> "*… pharmaceutical companies' specific registries… put all the data outside of the decision makers, into the manufacturers' hands, and then we still need to get it.*" (Provincial Key Informant, February 2010)

> "*What are we doing with the data that is received [from registries]…who is pooling this data, who is looking at it from a meta-analysis perspective? Are we relying on the company to do that for us, or are we doing it internally once the information's been received?*" (Provincial Key Informant, February 2010)

Monitoring a registry may allow Health Canada to learn about safety issues. However, as Carleton[11] notes, there are a variety of challenges that Health Canada faces in using patient registries:

- "Health Canada has no mandate to monitor the registries, unless identified in a regulatory requirement.
- The processes may delay access to drug[s].
- Data are not available for analysis, other than by the manufacturers.
- The only current response to problems is market withdrawal.
- Unless a follow-up study is under way, monitoring is confined to known ADRs.
- It can be difficult to determine cause-effect relationship between drug and reaction since many reports are based on single cases or case series.
- Multiple adverse events reported may reflect a single patient's experience or multiple patient experiences with a drug."

A final serious limitation of patient registries is that they do not include patients with the same clinical condition who are not taking the medication in question. The absence of such a control group threatens the validity of any observational findings.

(C) Health Canada's Current Authority

When post-market surveillance activities reveal signals that suggest there are safety concerns with a drug or biologic, Health Canada has the authority to implement risk mitigation strategies. These strategies fall along a continuum from a public alert or notice to health professional (e.g. a *Dear Health Care Professional* letter), to a request for product label changes, to—at the far end of the continuum—ordering the withdrawal of the drug from the market. However, the effectiveness of these strategies is often limited.

[i] A patient registry is a formal listing of all patients with a particular type of health problem.

Notices to health professionals: Health Canada reported to us that the type or source of evidence used, and the processes involved in determining the need for a particular risk communication about marketed health products are multi-factorial and involve various considerations. Factors that are considered in developing communications include, but are not limited to, the following:

- availability and reliability of the data;
- magnitude of the risk;
- seriousness of the event relative to the disease being treated;
- extent of patient exposure;
- potential to prevent or mitigate the risk in the patient population;
- relevance to clinical practice; and
- disproportionate impact on vulnerable populations (e.g. children or the elderly).

Health Canada also stated that the key principles for communicating risks about a marketed health product are: the right message should be delivered to the right persons at the right time; objective information about the safe and effective use of the products should support their appropriate use (and be considered a public health responsibility shared by all stakeholders); and communication of such information needs to be considered throughout the risk management process.[51]

The effectiveness of current forms of risk communication may be marginal at best. Between 2002 and 2005, health professionals were sent letters warning of serious adverse reactions associated with the use of the atypical antipsychotics in elderly patients with dementia. At the request of Health Canada, *Dear Health Care Professional* letters were sent for risperidone (Risperdal™) in 2002 and for olazapine (Zyprexa™) in 2004 by their respective manufacturers—Janssen-Ortho Inc. and Eli Lilly. A third letter was distributed directly by Health Canada in 2005, warning health professionals about increased risks for mortality associated with the use of any atypical antipsychotic in elderly patients with dementia. However, an analysis of prescriptions filled under Ontario's drug benefit program for senior citizens between 2000 and 2007 showed that the number of prescriptions for risperidone, olanzapine, and a third atypical antipsychotic, quetiapine (Seroquel™), did not decrease, but instead increased in the period after the warning letter was issued.[52]

> *"There's still a segment [of health professionals] that is ignoring the literature that's there, with regard to the warnings and when they should use or not use a product."* (Provincial Key Informant, March 2010)

Recently, the Marketed Health Products Directorate (MHPD) initiated a new study, in collaboration with Risk Sciences International and the University of Ottawa, to study the effect of selected *Dear Health Care Professional* letters on physician prescribing practice in Canada using interrupted time-series analyses with relevant Canadian prescription data from Intercontinental Medical Statistics (IMS) Health. Going forward, Health Canada will be focusing attention on studies designed to evaluate the effectiveness of its efforts on risk communication to Canadians.[53]

Labelling changes: Health Canada holds the power to request that changes be made to a product label, but does not have the power to force compliance. Health Canada, like the FDA and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, has preferred to negotiate with pharmaceutical manufacturers to address drug safety issues.[2] However, during the process of negotiation, the public continues to be exposed to the deleterious effects of the drug and the market authorization holder continues to earn profits from sales. As an example, Warner-Lambert and the FDA negotiated for 29 months before agreement could be reached for labeling changes to the anti-diabetic drug troglitazone (Rezulin™). During that time more than 60 people who were taking the drug died.[2] Subsequently the drug was withdrawn from the market.

Ordering market withdrawal: Although Health Canada has the authority under section C.08.006 of the Food and Drug Regulations to suspend a NOC/c and prohibit the sale of a drug[54] (Personal communication, Health Canada, January 2009), it has rarely exercised this power unilaterally and instead relies on consultations with the company involved. According to the Director General at the MHPD, the decision to withdraw a drug from the market is one that can rarely be made at the time a safety issue is first recognized. The process requires thorough analysis, including gathering of relevant safety information from the market authorization holders who are ultimately responsible for the safety of their products.[53]

(D) New Academic, Provincial and Federal Initiatives

Academic initiatives

The Pharmaceutical Outcomes and Policy Innovations Programme, based at the Children's & Women's Health Centre of British Columbia, has several projects designed to inform the drug regulatory process.[11] Examples include: (a) suspected pediatric ADRs reported to the Canadian Adverse Drug Reaction Monitoring Programme (b) ADR reporting within the Canadian Paediatric Surveillance Program and (c) the Genotype-specific Approaches to Therapy in Childhood (GATC) active surveillance network for adverse drug reactions. The GATC was to have been completed in December 2008, incorporating more than 1,000 serious ADRs and more than 7,000 controls. However, the program was deemed to be very useful and funding has been extended to 2014, and expanded from child health into other areas including mental health and cardiovascular health. The most innovative aspect is the comparative group of data collected from drug-matched controls (individuals who have taken the same drug but who don't develop ADRs). As of December 2009, more than 25,000 ADR cases and controls have been enrolled and relevant biomarkers (a substance used as an indicator of a biological state) for three serious ADRs have been identified.[55]

Several Canadian academic/research units provide post-market surveillance expertise to provincial drug plans on a contract basis or with year-to-year funding. Some, like the Institute for Clinical Evaluative Sciences in Toronto, the Population Health Research Unit at Dalhousie University, and the Manitoba Centre for Health Policy at the University of Manitoba, have researchers who focus on prescription drug issues within a larger research unit. At the units, some studies are funded by peer-reviewed grants and some are funded directly by provincial drug plans.

Provincial initiatives

The province of Alberta recently initiated the RAPPORT (Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics) program to monitor biologic agents used in the treatment of rheumatologic diseases.[56] Under the program, patients' access to therapy is conditional on participation in a pharmacovigilance study that assesses long-term effectiveness, safety, and cost benefit. The program—a partnership of academics, community rheumatologists, government and industry—is funded by industry but administered by government. To date, the program involves about 8,000 patients.[57] Similarly, in 2005, the Ontario Biologics Research Initiative (OBRI) was developed to gather information on the wide variety of treatments used for individuals living with rheumatoid arthritis with the goal of improving health outcomes.[58]

Federal initiatives

In July 2008, the federal government officially launched the Drug Safety and Effectiveness Network (DSEN), an arm's-length network sponsored under the granting authority of the Canadian Institutes for Health Research (CIHR), and in early 2009 it set funding for the DSEN at $32 million over the first five years and $10 million a year after that. The DSEN is designed to connect researchers throughout Canada in a virtual network to conduct post-market drug research that is independent of pharmaceutical companies[59] and stimulate research to study the impact of drug use in the real-world setting.[60] This network will look to make benefit-to-harm assessments of drugs that have been identified through a national prioritization scheme, selecting appropriate methodologies to support sustainable decisions for appropriate utilization of drugs. The establishment of the DSEN is in part a response to the parliamentary report *Post-Market Surveillance of Pharmaceuticals* (June 2008), in which continuous assessment of drug risk and benefit was recommended as part of a lifecycle approach to regulation of prescription drugs.[61] The specific objectives of the DSEN are (1) to increase the available evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers, and patients and (2) to increase capacity within Canada to undertake high-quality post-market drug safety and effectiveness research. (Further information about the DSEN is available at http://www.cihr-irsc.gc.ca/e/40269.html.)

> "*It [drug safety] is a highly relevant issue for Canadians, and particularly for consumers. But it's challenging, and hopefully from the DSEN perspective they will focus on some priorities and establish a culture of results.*" (Provincial Key Informant, February 2010)

As part of a separate initiative, in April 2008, the government unveiled new legislation (Bill C-51) that incorporated the principles of progressive licensing.[62] The bill was ultimately withdrawn, but Health Canada still appears to be committed to a system of progressive licensing. The aim of progressive licensing is to move from an "all or none situation"—either license the drug or don't—to a position where the risks and benefits of drugs are continuously assesed throughout their entire lifecycle. On its web page, Health Canada states that "*Progressive Licensing means that Health Canada would assess the benefits and risks of a product before and after it reaches the market, establishing a stable regulatory standard that reflects a lifecycle approach to drug regulation.*"[63] The promise of this new system is that ongoing re-evaluation of the risks and benefits of medications will pick up serious safety issues earlier and help to better target drug therapy. Under Bill C-51, Health Canada, acting through the minister of health, would have been given the authority to issue the market authorization for a drug subject to additional terms and conditions, and to suspend the authorization if the company did not follow through on its obligations. As well, clause 30 (3) in the bill would have allowed the minister to issue regulations necessary for the implementation of clauses in trade agreements such as *North American Free Trade Agreement* (NAFTA) article 1711.[64] Article 1711 deals with trade secrets,[65] and currently Health Canada defines the efficacy and safety data that companies submit as part of the drug approval process as a trade secret. (Previously, trade deals were mentioned as a reason for withholding information, but they were not referred to in legislation.) As noted earlier, although Bill C-51 was withdrawn, it appears that Health Canada remains committed to introducing a system of progressive licensing.

In 2006, Health Canada set up a multi-stakeholder Expert Advisory Committee (EAC) on the Vigilance of Health Products. The committee's mandate is to advise Health Canada *"on broad strategic policy issues including, but not limited to: how to improve the relevance and impacts of the marketed health products safety and therapeutic effectiveness policies and programs, educational programs, risk communication processes, regulatory advertising oversight issues, and ways it can strengthen its management and business practices."* [66] Summary reports of committee meetings are posted on the Health Canada's web site (www.hc-sc.gc.ca/ dhp-mps/ medeff/eacvhp-ccvrps/meet-reunion/index-eng.php). There is little information about how Health Canada uses the advice it receives from the EAC but the MHPD reports that, guided by input from the EAC, it recently launched guidelines and a new format for the writing of risk communications in more accessible language.[53]

In its correspondence with us, Health Canada reported that under its Canada Vigilance Program—health care professionals, medicines users and caregivers report ADRs to Canada Vigilance—it is developing a targeted monitoring strategy for newly marketed drugs. The goal of this strategy is to identify previously unknown or unrecognised adverse reactions as quickly as possible and to increase understanding of the safety profile of a new active substance (NAS)[j] by systematic monitoring over a specified time period. This strategy will undergo a pilot phase of two years, and during this time the NAS Monitoring List would remain an internal document. When the pilot phase is complete and evaluated, consideration will be given to possible next steps, such as whether it would be useful to publish a NAS Monitoring List in an attempt to increase reporting of adverse reactions to these newly marketed products.

Between 2006 and 2009, the federal government contributed $34.6 million to the Canadian Fabry Disease Initiative Enzyme Replacement Therapy Study, a trial set up to examine the relative usefulness of two different enzyme replacement medications for people with this rare disease. In addition to the federal government, Genzyme Canada Inc. and Shire Human Genetics Inc., and provincial and territorial governments contributed funding. Although the trial was designed to run for 10 years, the federal government withdrew its part of the funding at the end of October 2009. [67]

As part of another government initiative, provincial and territorial government drug information systems were, in July 2010, added to the certification program for Canada Health Infoway (*Infoway*), which is an independent organization funded by the federal government that invests in projects to help accelerate the development and adoption of electronic health record systems in Canada. As they are developed, the drug information systems support storage and retrieval of medication related information from a central database and are capable of supporting evaluation of drug utilization, an *Infoway* release states. Such systems could improve drug safety and effectiveness by monitoring patients' medications, their reactions to them, and any interactions between medications. As well, it could contain important information about a patient's conditions and the effectiveness of the medications for those conditions.[68]

[j] A *new active substance* is a medicine that has never been marketed in any form in Canada. Equivalent terms are new chemical entity and new molecular entity.

SECTION 2: INTERNATIONAL ACTIVE PHARMACOVIGILANCE

Pharmacovigilance is achieved through combined passive and active methods.[1] Key international regulators including the US FDA, the EU's European Medicines Agency (EMA), France's Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) all have the authority to request post-market studies, though the conditions under which a study can be required vary. Specific aspects of their pharmacovigilance strategies are legally mandated while others remain voluntary.

To generate and test hypotheses regarding marketed products, several nations—including France, New Zealand, the UK and the US—are adopting assessment approaches that incorporate academic expertise, and observational studies[k] that draw on health care databases. Observational studies have limitations because patients cannot be randomized into control and treatment groups, but the use of matched controls (individuals who have not used the treatment but are otherwise similar to those who have) can strengthen the validity of the findings. Observational studies can also be used to better understand safety signals and assist in refining hypotheses that can be tested in randomized controlled trials, making these studies an important element of the evaluative process.

The FDA, EMA, MHRA, ASSaPS and New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) are committed to developing relationships with research networks. Access to research networks will increase regulators' capacity to have their decisions informed by the real-world use and assessment of medicines in larger and more diverse populations than typical Phase III randomized controlled trials allow. In fact, regulatory agencies in the US (FDA), France (AFSSaPS) and New Zealand (Medsafe) already have administrative arrangements with a research network. The latter two incorporate the network into their regulatory framework, which enables them to commission research and establish closer links to academic research groups in order to enhance the regulator's capacity to investigate drug safety and effectiveness issues.

Active pharmacovigilance strategies in the EU, the US, the UK, New Zealand, and France are discussed in the next sections, with a focus on regulators' links with research networks.

(A) European Union

The EMA is responsible for the scientific evaluation of applications for European marketing authorization for medicinal products under a *centralized or mutual recognition procedure:* companies submit a single marketing authorization application to the EMA and, after it is granted, it is valid in all EU states. When the EMA approves a product, or grants major changes to a license, submission of a risk management plan is required as a condition for market authorization. The plan may include a risk management strategy when the drug has known safety issues, perceived health risks, the public health impact is high, or a new safety concern arises in the post-market period.

> *"If we think it's important enough to put what we call a 'specific obligation,' then it has to be followed completely. The only thing is, we don't use that measure—we use it to a certain extent—but we are more likely to use what we call a 'follow-up measure,' where the company makes an undertaking…the committee has to endorse it, and the company has to follow it."*
> (EMA Key Informant, June 2007)

Specific obligations or *follow-up measures* are attached to the risk management plan when limited data on efficacy and/or safety of a product is available at the time of approval. When entered as a condition of the market authorization, they must be followed by the company.

[k] An observational study draws inferences about the possible effect of a treatment on subjects, where the assignment of subjects into a treated group versus a control group is outside the control of the investigator.

> *"…If it's important enough, we can enter it into the conditions of authorization, as I said, a specific obligation for instance. And it has to be followed. If it is not followed, then we can have—we can take measures. For a lot of the studies, for instance, if there is a question about the feasibility of the study, or if there is some uncertainty, then we opt for a follow up measure, because that one gives us more flexibility on both sides. We are doing this, because there is [a] bit of uncertainty at the moment about the introduction of the new tools, you know the risk management plan, the studies that are linked to it. Because it is an early phase, we tend to take, if you like, the—we go along more with these follow up measures."* (EMA Key Informant, June 2007)

Market authorization holders commitments to monitor potential drug safety signals most often include a pledge to provide information to physicians on how to use new medications most appropriately, and may include establishment of a patient registry. The EMA's Committee for Medicinal Products for Human Use (CHMP)[l] may require market authorization holders to conduct post-authorization safety studies as part of the risk management plan and submit new data in the post-market period.[69] Observational studies are most often required but sometimes are not completed.

> *"What we found is that sometimes these studies are…not carried out because companies say that it is not possible to carry out these studies that have been requested in the EU."* (EMA Key Informant, March 2010)

The European system is complicated because EU and national legislation are not always harmonized. For example, the development of patient registries, the conduct of observational studies, and data privacy laws are still under national legislation. This situation can create challenges in conducting post-market studies, agreed to at the EU level, that draw on national health care databases.

Thus, although the EMA has the authority to enforce compliance in the completion of post-market studies,[70] to date these measures have not been fully used. For example, penalties have not been applied when studies have not been completed. As one EU informant told us, post-market commitments are tracked at the EMA, which sets timetables for committee review of the commitments, and the EMA has various options for taking action for pharmacovigilance non-compliance.

> *"But in practice, when there are delays in meeting commitments, the issue is raised with companies, and the timetable can be changed."* (EMA Key Informant, June 2007)

The requirement for risk management plans represents a step toward addressing safety risks, but implementation is partial. Eighteen EU risk management plans approved between November 2005 and May 2007 were examined (nine for biologicals and nine for small molecules). A total of 169 safety concerns were identified including 50 (29.6%) important identified risks, 73 (43.2%) important potential risks and 46 (27.2%) important missing information notations. Forty-seven post-authorization safety studies were proposed to examine these safety concerns. No full study protocols were submitted; 26% involved a limited study protocol, 33% a study synopsis, 37% a short description, and 4% a commitment without further information. A substantial minority of the patients to be included in the post-authorization safety studies did not come from the EU, making generalizability a potential issue.[71]

In 2004, the EMA began to implement, over a four-year period, legal commitments it had made with respect to the transparency of its operations. The agency had already initiated higher degrees of transparency than many other jurisdictions when, in the 1990s, it began publishing on its website European Public Assessment Reports for pharmaceutical products that received market authorization. However, the independent drug bulletin *Prescrire*, which submitted 81 requests for documents between 2005 and 2008, found the EMA was reluctant to divulge information and slow to respond. And despite a regulation that stipulates that overriding public interest justifies disclosure of information, *Prescrire* found that the EMA censored and limited information on adverse drug reactions. When *Prescrire* requested information on rimonabant (Accomplia™), an anti-obesity drug that has since been withdrawn from the market, it was sent a report on the drug by a Swedish agency in which 65 of 68 pages were redacted and illegible. The redaction was justified on the grounds of the protection of commercial interests; the Swedish agency claimed that the commercial interests of the company would be compromised by the release of the safety information.[72]

[l] See CHMP website (www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7a) for more details about CHMP responsibilities.

Requirements for public disclosure are integral to an initiative aimed at offering greater support for post-market studies in the European Union. The EMA is working with the European Commission's Directorate General for Research to establish priorities for commissioned research, some of which may be undertaken by the EMA sponsored network of research centres, referred to as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

The EMA is supporting the development of the ENCePP: a network comprising institutions located throughout the EU that includes university-based, hospital-based and government-based centres with a broad scope of research expertise—including pharmacoepidemiology, and pharmacovigilance—in disease-specific therapeutic areas.[73, 74] ADR reporting, prescription event monitoring, health care claims, pharmacy dispensing, case-control surveillance, and prospective studies databases are available to researchers through the ENCePP network. Researchers also have access to data from primary care electronic patient and exposure registries. The network will be available to conduct post-market epidemiologic studies commissioned by market authorization holders to assist in identifying, characterizing, and assessing risks related to medicines in order to enable more active pharmacovigilance and to support the specific obligations and follow-up measures agreed to in their risk management plans.

As a new EMA initiative, the ENCePP was developed without a legislative mandate or public funding. Industrial sponsors will be responsible for funding all studies contracted to ENCePP research centres. Both the research centre investigators and the industrial sponsor must abide by its code of conduct in order to be considered an ENCePP study. EMA staff are working collaboratively with the academic centres in the network to make it possible for ENCePP studies to be carried out starting in 2010.

ENCePP committees

The ENCePP formed several committees, including one that established a checklist of methodological research standards and another that developed a code of conduct.[73] Both the checklist and the code were posted on the ENCePP website, and public consultation was sought. More than 350 comments were received from stakeholders, including industry, academics, regulatory agencies, and patient organizations.[75] The ENCePP code of conduct is a set of business rules that guides the company funding the study, and the research centre undertaking it, to maximize independence and transparency. The code covers such areas as the study contract, protocol development, data ownership, interim analyses, publication of results and conflicts of interest. The network's checklist of methodological standards is intended to ensure scientific rigour. A master guide will cover all important aspects of observational research, and be updated on a regular basis. It will be publicly available in order to promote high standards. ENCePP studies will be registered and made publicly available.[73]

ENCePP studies

ENCePP-designated studies are an important pharmacovigilance strategy because they conform to the rigorous research standards embodied in the methodological standards checklist, and because investigators have the independence to accurately present and publish the study results. In addition, all ENCePP studies are registered in a public database prior to commencement, and the public will be able to follow studies to completion.[74] This procedure will discourage the possibility of a sponsor not making study results publicly available if a product does not show a clear benefit or demonstrates important adverse effects.[76] Sponsor-funded research will be regarded as an ENCePP study if the lead investigator at the research centre agrees to follow the code of conduct, completes the checklist for methodological research standards in the study protocol (this includes the definition of the study question and outcome, how the exposure will be measured, and how issues of potential confounding are addressed), agrees to register the study in a public database of post-market studies, and sends the EMA the protocol before the study starts.[73, 74] The code of conduct also places ownership of the study data with the research centre conducting the study:

> *"Intellectual ownership by the parties directly involved in the planning and conduct of the study as well as the analysis and interpretation of the study data should be taken into account and should be provided for in the contract."* [73]

> *"A full report of all results with a scientific or public health impact must be made publicly available without unjustified delay. In case of a (suspected) public health impact, relevant legal provisions shall be followed and the respective regulatory authority(ies) shall be informed forthwith and in advance of publication."* [73]

Although the EMA cannot mandate that industrial sponsors contract ENCePP research centres to conduct required post-market studies, it encourages ENCePP's involvement. The EMA publishes an inventory of ENCePP research centres and their areas of research expertise.

EU post-market study funding

The European Commission, the executive body of the European Union with one commissioner for each member state, also funds post-authorization safety studies through its Framework Programme, which is supported by the Directorate General for Research. Under the Directorate General for Health and Consumers, the EMA (which was formerly under the Directorate General for Enterprise) consults with its Pharmacovigilance Working Party and the CHMP to develop a list of safety research priorities that involve either a class of drugs or off-patent substances. In the case of a single product with a safety issue, the market authorization holder is asked to carry out a study to address the concern through either a specific obligation, or a follow-up measure as part of the market authorization. However, when a class of products is at issue, the EMA's experience is that it can be a challenge to get companies to agree on a research protocol and that the process may take an inordinate amount of time. Moreover, for an off-patent product, it would not be in the commercial interest of any pharmaceutical company to carry out a safety study.

Funding for the European Commission's Framework Programme is approximately € 3–5 million for each study over five years and does not normally cover randomized controlled trials. Moreover, the program is not designed to address safety issues that require urgent elucidation, as it involves a lengthy request for research proposals process. After the request for proposals (RFP) is published in the *Official Journal of the European Communities*, research centres have three months to collaborate to form a consortium and prepare and submit a proposal that is appraised by the European Commission. It can take five years from the time of the call for proposals to the completion of the research.

When proposing topics, the EMA considers the public health impact of the research, including the seriousness of the safety issue and how widely the class of drugs is used.

The Framework Programme is not set up to investigate safety issues of immediate concern and the EMA has only modest funds (about €200,000 a year) to support urgent safety studies. For these urgent studies, the EMA is not required to publish the RFP in the official journal; instead it can send it to a shortlist of qualified centres (previously selected following a call for expressions of interest published in the official journal) and choose among the proposals received. A selection committee assesses the centres on the basis of several criteria including their expertise and their publications. The pre-qualified list of research centres thus compiled is valid for a three-year period. This procurement process funds studies up to a maximum of €125,000. As with the Framework Programme, the post-market safety research funded by the EMA covers only observational studies.

The CHMP decides which of the drugs they are evaluating require an updated risk management plan, and further post-market safety study, or safety monitoring. Priority areas funded through the European Commission Framework Programme are guided by the EMA, which puts forward a list of drugs and related safety issues developed by its pharmacovigilance working party. The CHMP will subsequently consider and modify or adopt the list, specifying which classes of drugs, linked to specific safety issues, are priorities for further study. In the case of the EMA safety fund, the safety issue to be studied is decided with or without consultation with the Pharmacovigilance Working Party.

Some of the European national authorities also fund their own research into the safety of medicines. For example, the regulatory authorities in France, Italy and the UK sponsor some research into the safety of drugs as do Sweden and Spain. (EMA Key Informant, March 2010)

European Commission proposals to change pharmacoviligance

In December 2008, the commission published a proposed regulation and directive that included an increased use of risk management systems, elimination of public funding required for pharmacovigilance activities, the creation of

a supra-national database for collecting ADRs, and the establishment of a European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC). A group of leading European public interest organizations issued a statement warning that the proposed changes could increase the likelihood of dangerous drugs being given market authorization, cede the public's role in pharmacovigilance to drug companies, tighten drug companies' control over the interpretation of data (including ADRs) and, in the form of PRAAC, create a body with no authority and no autonomy. The group expressed particular concern that the central role of the existing national and regional pharmacovigilance centres would be undermined, because instead of reporting to these centres, health care practitioners and patients would be allowed to report adverse events solely to drug companies.[12] The status of this proposal is unclear at this stage.

(B) United States

Unlike the EU, the FDA in the United States does not require a risk management plan as a condition for drug approval. The FDA may require drug manufacturers to conduct post-market studies to address specific concerns, but only when adverse drug events trigger new safety signals that require further study to better elucidate their significance.

> "*So the first event is to identify some post-approval safety issue: either something that was a lingering concern at the time of approval, or something that's come up since approval, and we look at the available data. Sometimes those will come from spontaneous adverse event reports, sometimes somebody will find a publication in the literature, sometimes companies will be doing clinical trials to extend indications, or for other reasons, and find an unexpected safety finding. The source can come from anywhere.*"
> (FDA Key Informant, March 2010)

The FDA Amendments Act (FDAAA) increased the FDA's responsibility to adopt a more proactive approach to pharmacovigilance by enhancing its authority to actively investigate pre- and post-market drug safety. In addition to FDA authority to contract research centres to independently investigate safety signals, new programs (e.g. the Sentinel Initiative) have been established and new powers have been granted to the FDA to increase active post-market risk identification and analysis. The Sentinel Initiative will develop a national electronic system for monitoring product safety by developing methods to access disparate health data sources and by establishing a post-market risk identification and analysis system (Figure 1). The FDA also gained authority to issue fines in order to enforce commitments made by drug sponsors to conduct post-market studies and clinical trials, make product labeling changes, and create Risk Evaluation and Mitigation Strategies (REMS). The FDAAA also included amendments to the Prescription Drug User Fee Act (PDUFA), referred to as PDUFA IV[m] which allow user fees to be directed to acquire data and to fund the development of best practices in epidemiology. The FDA engages in a consultative process to determine the need for post-market studies. As of May 17, 2010, the FDAAA has led the FDA to:

- issue over 200 letters that outline post-market requirements to assess safety issues for drugs and biologics. The post-market requirements, and the timeframes to conduct the studies, are enforceable.
- use its new authorities to require safety label changes 35 times. Most of the safety label changes were invoked for classes of drugs or biologics. For example, the FDA required safety label changes to add the risk of neuroleptic malignant syndrome to the prescribing information for selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.
- require REMS to ensure that the benefits of a drug outweigh its risks. In the first two years of the implementation of the FDAAA, the Center for Drug Evaluation and Research (CDER) has approved 116 REMS—78 of which require only a medication guide, with the balance (38) requiring elements to ensure safe use. Twenty-seven of the 38 require a communication plan.[77-79] (Updated through FDA correspondence)

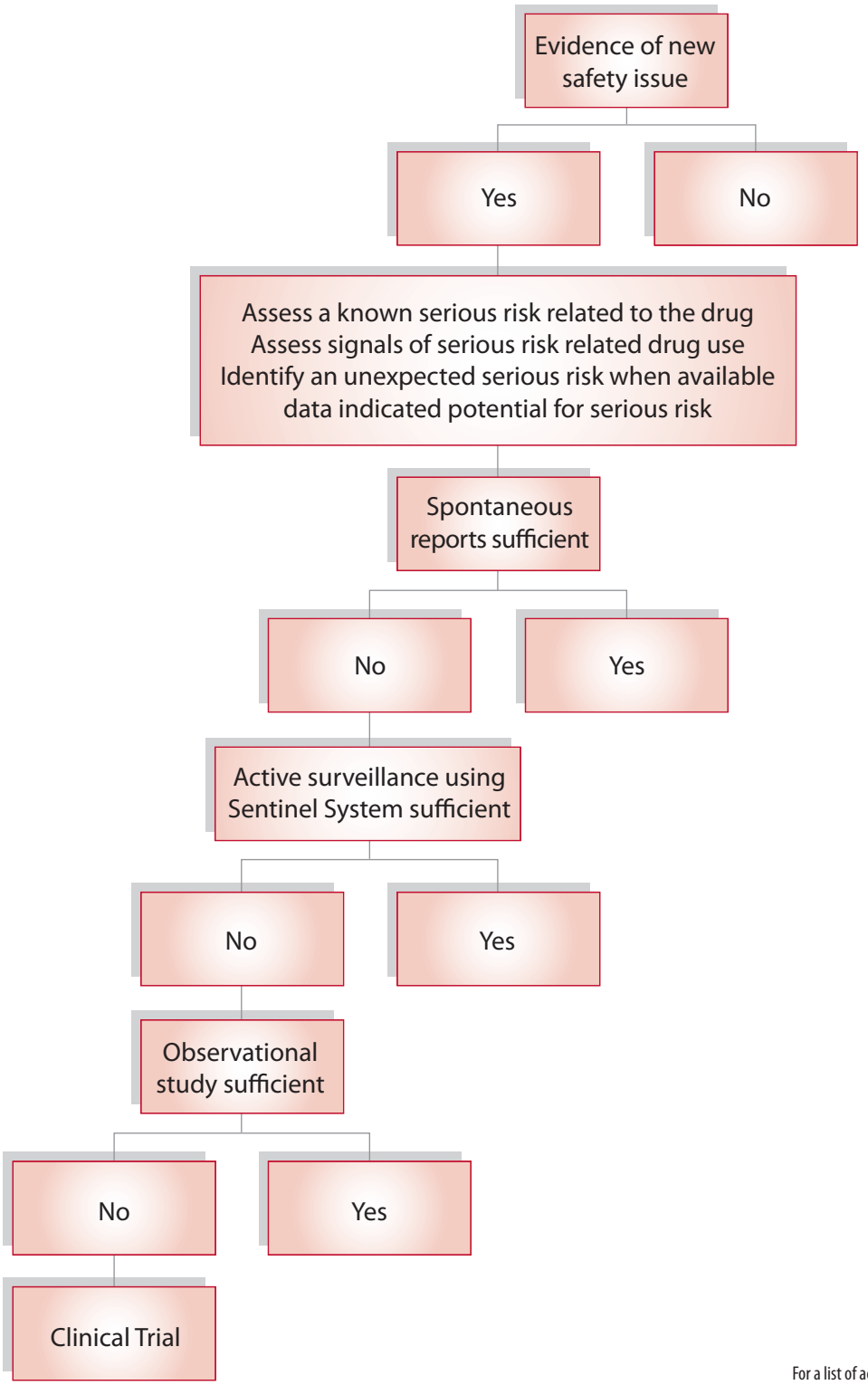
Establishing the need for post-market studies

Under FDAAA, before the FDA can require a post-market study, it must first determine if monitoring spontaneous reports of adverse drug events is sufficient to answer safety questions or if setting up active surveillance is necessary. The FDA thus addresses each safety concern on a case-by-case basis. Figure 1 outlines the process by which the FDA determines if it can impose a post-market requirement on a company.

[m] The Prescription Drug User Fee Act (PDUFA) was originally enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV). It authorizes the FDA to collect fees from companies that produce human drug and biological products; the fees are used to expedite the drug approval process.

FIGURE 1: GUIDELINES FOR CENTRE FOR DRUG EVALUATION AND RESEARCH (CDER) POST-AUTHORIZATION STUDIES

This figure describes the guidelines set by FDAAA for use by CDER to determine whether to impose a post-marketing requirement on a pharmaceutical company.



For a list of acronyms, see page 2.

> *"We can't require anything if spontaneous reports, which we have, are sufficient to answer the question. And then it says, if they're insufficient, can we answer the question using this active surveillance system that the law sets up, and that doesn't exist yet, that's what we are calling the Sentinel system.… And so then, if those two can't do it, then you go to an observational study, but if you find that insufficient, then you go to clinical trial. We don't have formal criteria for that."* (FDA Key Informant, March 2010)

The FDA enhances its pharmacovigilance expertise by forming advisory committees to provide information to assist with decision-making. A FDA advisory committee composed of external experts will determine the type of study needed and make a recommendation to the FDA. Advisory committees are convened under the Federal Advisory Committee Act. A recent example of FDA decision-making that was informed by the input of an expert advisory committee concerned a class of drugs referred to as long-acting ß-2 agonists, used for asthma. Recent safety signals, meta-analyses and clinical trials had suggested increased asthma-related hospitalization, intubation, and death associated with the use of these drugs, despite their benefits.

> *"Their use has changed since they were first approved so we said, 'We think you need to study this more,' and a prior advisory committee had endorsed that. And so the question is, what would that [study] look like?"* (FDA Key Informant, March 2010)

A joint meeting of the Pulmonary and Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held to determine the type of study design that would clarify the risks of ß-2 agonists. It included experts in pulmonary and allergic diseases, and representatives from several areas of drug safety: epidemiology, surveillance, risk communication, pharmacy systems and toxicology. (Committees generally also include a biostatistician, a consumer representative, and a patient representative.) The two committees recommended a randomized controlled trial.

> *"…they generally endorsed the clinical trial approach to this but the burden is on us to explain why we think somebody has to be at a higher step on that scale than the lower [why a randomized control trial is required rather than an observational study] but we don't have a formal criteria at this point. It's a little too new for us to have that."* (FDA Key Informant, March 2010)

FDA advisory committees have frequently been criticized for including members with significant conflicts of interest such as, for example, individuals who received funding from the companies whose drugs are being studied, or who conducted company-funded research of the drugs being studied.[80] One example is the composition of the committee that voted in favour of continuing to allow celecoxib (Celebrex™), rofecoxib (Vioxx™) and valdecoxib (Bextra™) to remain on the market; ten of the 32 panel members had consulted in recent years for the drug makers. *"If the 10 advisers had not cast their votes, the committee would have voted 12 to 8 that Bextra™ should be withdrawn and 14 to 8 that Vioxx™ should not return to the market. The 10 advisers with company ties voted 9 to 1 to keep Bextra™ on the market and 9 to 1 for Vioxx's™ return."*[81] Provisions in the FDAAA have led to some new restrictions on conflicts of interest.

Governance of active pharmacosurveillance

The FDA's Office of Surveillance and Epidemiology (OSE) received increased funding with the enactment of the Prescription Drug User Fee Act (PDUFA) IV.[n] This enabled an increase in its staff and training.[82] In 2009, the US GAO added a new reporting area—"protecting health through enhanced oversight of medical products"— to its regular series of reports on high risk-areas.[83] A key GAO recommendation was for the FDA Commissioner to develop a plan to transfer more responsibility to the OSE.[84] The GAO found that the FDA tends to rely on sponsors of drug products to inform the FDA of safety issues rather than seeking the information on its own. Moreover, it found that the FDA had not followed up with drug sponsors on their commitments to conduct post-market studies, about half of which were never completed.[14]

[n] The FDAAA allows the FDA to use its PDUFA IV fees to fund the development of epidemiology best practices and for data acquisition ($7 million in fiscal 2008, increasing to $9.5 million in fiscal 2012), new trade name drug review ($5.3 million in fiscal 2008, rising to $6.5 million in fiscal 2012), and risk management and communication ($4 million in fiscal 2008, rising to $5 million in fiscal 2012). The PDUFA IV Drug Safety Five-Year Plan can be viewed at *www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM216354.pdf.*

Epidemiologic (observational) studies commissioned by the FDA and conducted by independent research centres will be informed by the FDA's guidance documents on best practices. Because the FDA also has authority to require product sponsors to conduct observational studies, pharmaceutical companies and the research centres they contract to conduct the studies will also be guided by the FDA's best practices. The OSE is in the process of developing guidance documents on how to use large administrative and other health care databases to answer drug safety questions—a commitment made under PDUFA IV—and convened a public meeting on the issue. A priority for best practice guidance is to develop "*better epidemiologic methods to handle confounding in observational data.*" (FDA Key Informant, March 2010) This refers to the validity of observational studies, focusing on the ability of researchers to attribute an adverse effect to a drug product or a class of drug products with a certain level of confidence.

> "*We envision, especially with the FDAAA requirements … that we can require these observational studies, that firms will be doing this more and more, and so that is why the best practices guidance.*"
> (FDA Key Informant, March 2010)

FDA auditing of the data used in the observational studies it commissions could also be considered a best practice. A key informant from an academic research centre noted that the FDA requests the data and re-analyzes it, an important audit function that "*…helps us to really focus extra hard on getting things right. And that is helpful.*" (DEcIDE Key Informant, March 2010)

Enhancing post-market research capacity

Sentinel System

The FDA has adopted a multi-pronged approach to pharmacovigilance, developing the Sentinel System framework to support its own ability to query large databases, and combining this with contracts with research centres to have them address specific issues.

Section 905 of the FDAAA directed the FDA to launch the Sentinel Initiative in 2008 in order to enhance its existing internal post-market safety surveillance systems, which consist primarily of the passive collection of information through ADRs and other documentary analysis. The Sentinel Initiative will enable queries of electronic health care data systems in a secure manner. The goal of Sentinel is to attain access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012, and this requires the FDA to work closely with partners from public, private and academic sectors. Questions will be sent to participating centre researchers who will evaluate their data and send results summaries to the FDA, in accordance with privacy and security safeguards. Sentinel will give the FDA the capacity to proactively monitor drug safety issues.[79]

The FDA also formed a Federal Partners Working Group to engage federal agencies involved in initiatives that are complementary to the Sentinel Initiative. This working group includes representatives from the:

- Agency for Healthcare Research and Quality
- Centers for Disease Control and Prevention
- Centers for Medicare & Medicaid Services
- Consumer Product Safety Commission
- Department of Defense
- Department of Veterans Affairs
- Health Resources and Services Administration
- Indian Health Service
- National Institutes of Health
- Office of the National Coordinator
- Office for Human Rights Protection
- Substance Abuse and Mental Health Services Administration

Reports developed by the working group will inform the Sentinel Initiative and be publicly available on its website. The FDA gathered advice from the public by holding meetings on the development of Sentinel and by piloting a discussion forum on the Sentinel website.[79]

The FDA is also developing two "mini" Sentinel Systems. Mini Sentinel System I will offer the FDA the ability to evaluate safety concerns and understand potential issues that may arise in developing the Sentinel System. It will contract a private organization to serve as a coordinating centre to launch a consortium of automated health care databases to respond to FDA queries. [79]

> "*The mini sentinel will pool several databases together in order to maximize the sample size for each study and that might be of interest to Canada of course with all the provincial databases and what kind of strategies are employed in order to respect the privacy issues that these have because they don't want to dump all the data into one big database. There are firewalls and …only the relevant data will flow out to the FDA.*" (DEcIDE Key Informant, March 2010)

Under the Observational Medical Outcomes Partnership, which was established under the FDAAA, the FDA is developing a partnership with the Foundation of the National Institutes of Health and the Pharmaceutical Manufacturers of America. Funding from the partners will support a series of feasibility studies. This partnership is supporting the creation of a mini Sentinel II, in which the FDA and the Centers for Medicare & Medicaid Services are developing projects that analyze Medicare data to better understand post-market safety of drug products. The FDA has also developed interagency agreements with the Departments of Defense and Veterans Affairs to advance the science of pharmacovigilance by developing methods that strengthen the FDA's ability to detect safety signals. Mini Sentinel II could offer a prototype of what is possible with the larger scale Sentinel System. The FDA has also commissioned a legal evaluation of state laws in the 50 states to assess whether they prevent the use or disclosure of health information beyond what the federal laws require.[79]

Contracts with academic centres

The FDA forms partnerships and enters into cooperative agreements for the purpose of enhancing research expertise or for gaining access to databases that it can use for drug safety research.

> "*The FDA needs these questions answered and we can't do it ourselves, so we do it in collaboration with outside groups that have both the data and the expertise.*" (FDA Key Informant, March 2010)

The FDA has developed a framework to commission independent research through two networks—the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network and the Centers for Education and Research on Therapeutics (CERTs) network—and contracts with other research centres. Contracts expand the agency's ability to rapidly evaluate newly marketed drugs.[85]

The CERTs model involves investigator-initiated projects that are funded for five-year periods on a peer-review research grant basis in response to requests for applications announced by the FDA or the Agency for Healthcare Research and Quality (AHRQ).[o] The CERTs network, created in 1999, is composed of a coordinating centre and 14 research centres based in 12 universities. Network studies span a range of areas; those most relevant to the FDA are based on observational pharmcoepidemiological population-based research.

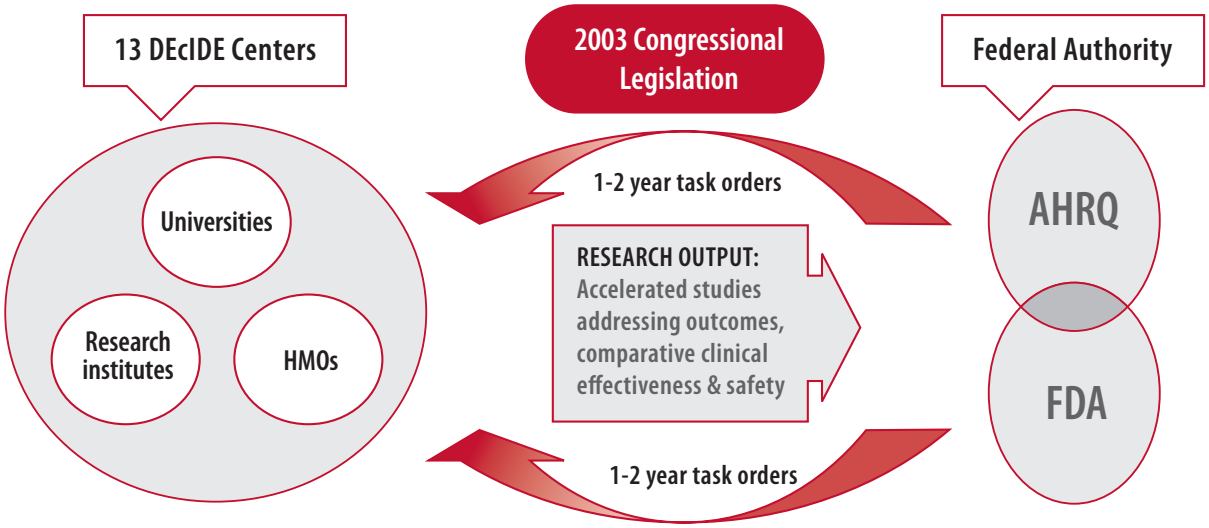
The DEcIDE network (Figure 2) was created as a result of the Medicare Modernization Act (MMA) of 2004, which extended Medicare coverage to medications when Medicare Part D became active in 2006. The MMA included funding for comparative medical research. The AHRQ was designated to manage the comparative research and used the funding to create the DEcIDE network, which is based in academic institutions that draw on service providers' health care plan databases. DEcIDE projects are commissioned by the AHRQ or the FDA to address research questions and designs with a turnaround time of one to two years. The main purpose of the DEcIDE network is to investigate the comparative clinical effectiveness, safety, and appropriateness of health care products and services.[86]

The FDA also supports six Evidence-Based Practice Centers (EPCs) through contracts with pharmacoepidemiology research centres. The EPCs summarize evidence that is already available through meta-analysis to support the FDA's decision-making process. (In contrast, the DEcIDE research centres generate new evidence.)

As well, the FDA has established a Memorandum of Understanding with the Department of Veterans Affairs (VA) to promote better data sharing between the FDA and the VA. In addition to the DEcIDE and CERTS networks, and the EPCs, the FDA also contracts individual research centres to conduct epidemiologic studies.

[o] The Agency for Healthcare Research and Quality is a part of the United States Department of Health and Human Services that supports research designed to improve the outcomes and quality of health care, reduce its costs, address patient safety and medical errors, and broaden access to effective services.

FIGURE 2: DEVELOPING EVIDENCE TO INFORM DECISIONS ABOUT EFFECTIVENESS (DEcIDE)



For a list of acronyms, see page 2.

Universities include: Johns Hopkins University, University of Colorado, University of Maryland at Baltimore, University of North Carolina at Chapel Hill, Brigham and Women's Hospital, University of Illinois at Chicago, Vanderbilt University, Duke University, University of Pennsylvania School of Medicine

Research Institutes include: Acumen, LLC, Outcomes Sciences, RTI International

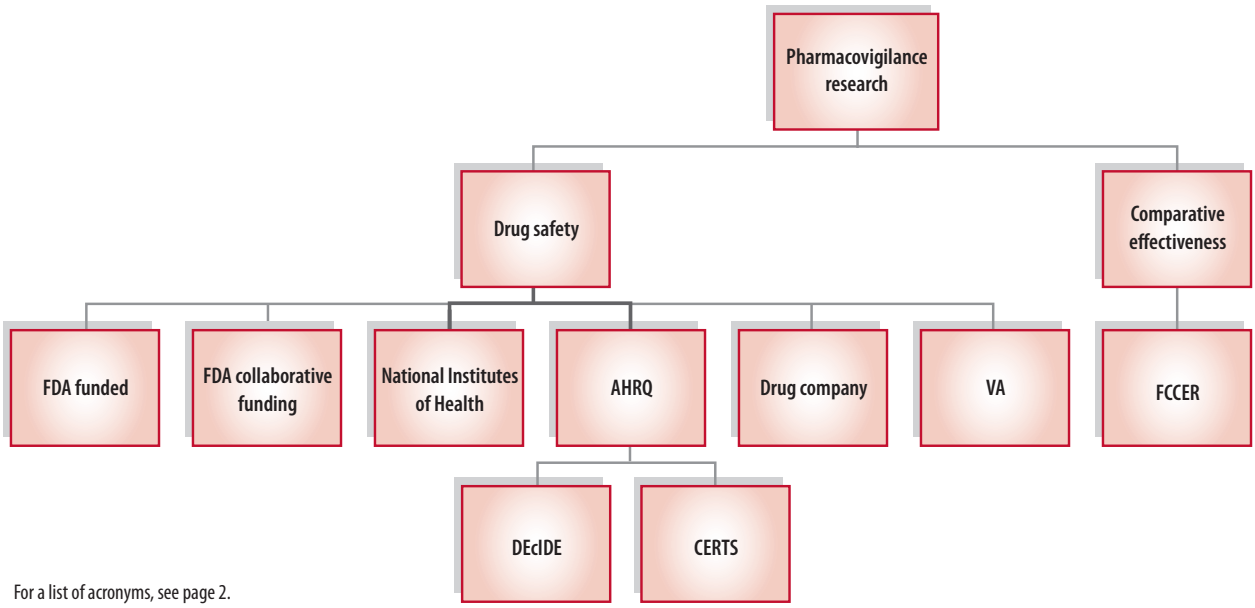
Health Maintenance Organizations (HMOs) include Harvard Pilgrim Health Care

> "*We do have outside contractors who work on epidemiology studies with us but we are paying them through a public competition. We would put out a request and whoever wants to apply applies…we'll review these applications and select the best one. And they can work together, like the study on attention deficit hyperactivity disorder is across multiple contractors and they figure out how to work together…we haven't set up that kind of network. Now how Sentinel works may change that model, but I think we still have yet to see that.*"
> (FDA Key Informant, March 2010)

The US offers the highest level of public funding in absolute dollar amounts to support active pharmacovigilance as compared to other countries studied. Pharmacovigilance research is funded by the FDA directly or through collaborative partnerships (i.e. FDA/ AHRQ collaborative study of drugs used in the management of ADHD involve multiple contractors), drug company user fees (PDUFA IV fees fund epidemiology best practices, data acquisition, new drug trade name review and risk management and communication), the Department of Health and Human Services (funding for health information technology), the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). In addition, the American Recovery and Reinvestment Act of 2009[87] provided $1.1 billion to establish the Federal Coordinating Council for Comparative Effectiveness Research (FCCER). The act also allocates funding for the development of a Patient-Centered Outcomes Research Institute to address gaps in the current evidence related to pharmaceuticals, particularly with respect to funding for research on the comparative effectiveness of drugs. (Figure 3)

The Eisenberg Center, funded by the AHRQ, is responsible for communicating the results of the research produced by the DEcIDE network and the EPCs through the creation of guideline documents for physicians and patient information sheets. The communication process is often referred to as research translation.

FIGURE 3: FUNDING STREAMS FOR PHARMACOVIGILANCE RESEARCH IN THE US



For a list of acronyms, see page 2.

(C) United Kingdom

The UK Medicine and Healthcare Products Regulatory Agency (MHRA) was restructured in March 2006. A new division responsible for pharmacovigilance was created, MHRA's access to research evidence to aid harm:benefit analysis was increased, and multi-disciplinary teams were established to improve communication among responsible agency units and support decision-making throughout a drug's lifecycle.[88] The reorganization was prompted by increases in agency tasks and responsibilities and EU regulations that require MAHs to submit RMPs.

> "*With reorganization you know exactly who is responsible for what and who to talk to.*" (MHRA Key Informant, July 2007)

The new divisions include the Vigilance and Risk Management of Medicines (VRMM) Division and an Information Processing Unit (in the Information Management Division). Product lifecycle assessment teams are able to advise across divisions.

The MHRA also formed a number of independent advisory bodies—made up of professionals, and lay and patient representatives—to advise the minister on issues related to the regulation of medicines. These bodies include the Commission on Human Medicines[p] and the Independent Scientific Advisory Committee.[q] The advisory bodies in turn have formed expert advisory groups (EAGs), focusing on issues such as pharmacovigilance, clinical trials and pediatrics.[88, 89]

The VRMM Pharmacovigilance Risk Management Section engages in epidemiological research and produces reports for its EAG. The VRMM's Pharmacovigilance Signal Management staff provides raw ADR data to external researchers and works with them to guide their applications to ensure that the data is used effectively to conduct independent research. The resulting reports and research findings are submitted to the Pharmacovigilance EAG.[88] The MHRA does not have to act on the advice it receives from its independent advisors, although the advice is generally accepted.

[p] The Commission on Human Medicines is a committee of the UK's Medicines and Healthcare products Regulatory Agency. It was formed in October 2005 by the amalgamation of the Medicines Commission and the Committee on Safety of Medicines. The CHM's responsibilities include advising UK government ministers on matters relating to human medicinal products, giving advice in relation to the safety, quality and efficacy of human medicinal products, and promoting the collection and investigation of information relating to adverse reactions for human medicines.

[q] The role of the Independent Scientific Advisory Committee is to review the scientific merit of proposals for research using data from the MHRA General Practice Research Database (GPRD) and Yellow Card Scheme database.

Products that present particular risks are monitored through patient or drug registries and disease registries in the UK. Patient registries are managed by the market auhorization holder. For example, the use of the antipsychotic clozapine is restricted to a sub-population of patients; the function of a *patient registry* is to monitor whether a patient has met the criteria for using the drug; only patients who are already taking the product in question are on the registry. From a research perspective, since patient registries do not include a control group, they are of limited utility. (DeCIDE Key Informant March 2010)

Disease registries support more rigorous epidemiologic research than patient registries because studies can be designed that categorize subjects into treatment and control groups, thus enhancing the validity of the study. The primary function of *disease-specific* registries is to monitor harm: benefit throughout the lifecycle of a drug. These registries are run by physicians, academics, professional organizations, and government. For example, the British Society for Rheumatology runs the Biologics Register and the Department of Health runs the National Cancer Registry. Hospitals may also be involved in the administration of a registry. Disease-specific registries provide ongoing, long-term data to better understand the disease and the real world use of various drug therapies, and to assist in identifying rare side effects.

The National Institute for Health and Clinical Excellence (NICE) in the UK conducts post-market evaluation of drugs at the direction of the Ministry of Health in order to make recommendations regarding public funding for drugs. The NICE may make a recommendation that further research should be conducted when, as a result of their appraisal, they believe that the current evidence base is insufficient to justify National Health Service funding. The NICE may recommend that a drug be made available on an *only* in research basis, which means funding for the drug is conditional on patient enrolment in a well-designed research study. In addition to its only in research recommendation, the NICE may make recommendations regarding "*what kind of research designs to suit NICE might be embodied in some clinical research*" and may engage in discussion about endpoints.

> "*Did the patient drop dead or how long does it [the research] go on? Does the dosage have to be increased with increasing body mass, for example if you're looking at something for children? That is going to have quite an implication for cost and so forth and so on.*" (NICE Key Informant, February 2010)

The NICE has not yet fully realized the potential of the only in research recommendation "*mainly because it's a way of making a recommendation which is relatively new. …NICE didn't do this originally. And they took a little while to learn I think how to do it.*" (NICE Key Informant, February 2010)

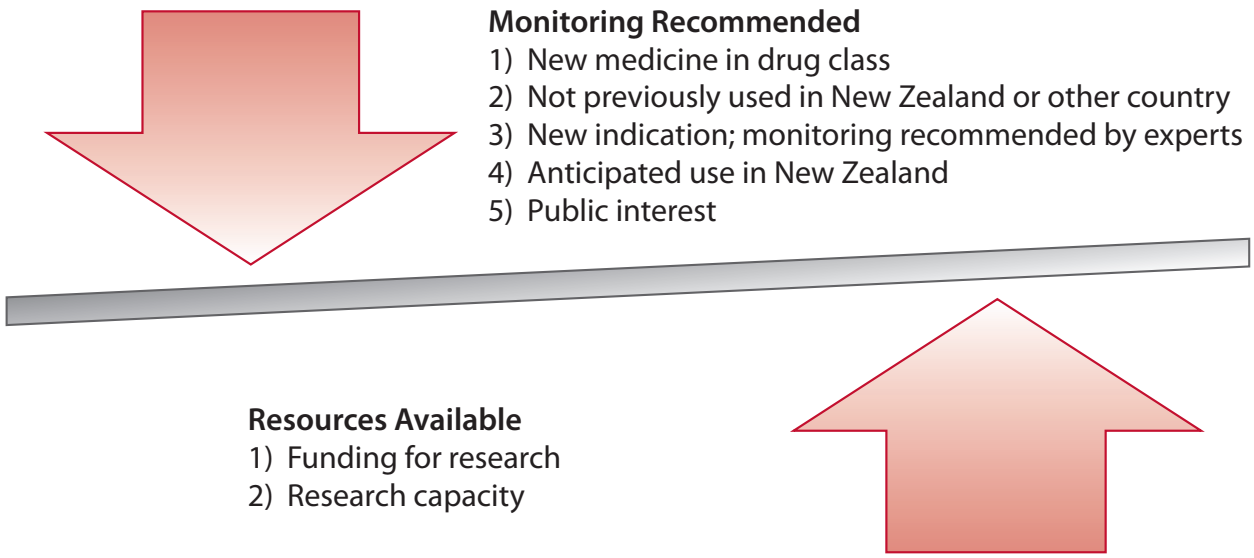
Importantly, the NICE does not have the capacity to fund the research that it recommends. NICE recommendations are communicated to the Medical Research Council and drug companies, for them to consider funding the research. If an outside source of funding is not found, the research is not undertaken.

(D) New Zealand

In New Zealand, the Medicines and Medical Devices Safety Authority (Medsafe) commissions all post-market studies by contract through the National Pharmacovigilance Centre located at the University of Otago in Dunedin. Medsafe informs the sponsor of its decision to commission a study and oversees a limited number of post-market studies through its contracted research centre. Medsafe prefers to conduct the studies through its research centre rather than have the industry involved. It has no legal mandate to request studies from drug sponsors.

The Intensive Medicines Monitoring Programme (IMMP) based at the University of Otago undertakes prospective observational cohort studies of selected new drugs. Historically, a medication was selected for intensive monitoring if it was a new medicine in the class, had not previously been used in New Zealand (or elsewhere), had a new indication, or was a medicine of interest. (Figure 4) The anticipated wide use of the medicine and public interest might also be factors when deciding whether to include a drug for intensive monitoring.

FIGURE 4: FACTORS CONSIDERED FOR INTENSIVE MONITORING OF DRUGS IN NEW ZEALAND



Today, the process in New Zealand is more *ad hoc*, with consideration given to whether sufficient resources are available to conduct the post-market studies.

> "*…now it's an ad hoc process but it's still the requirement or the expectation that it's a new medicine in a new class and there's a special reason to do so…. but I guess one of the other factors that begin to come into play now is the resources availability to do the monitoring for these medicines.*" (National Pharmacovigilance Centre and Centre for Adverse Reactions Monitoring, Key Informant, February 2010)

Currently only one IMMP study—on the smoking cessation therapy varenicline (Champix™)—is ongoing.

New Zealand is considering developing an enhanced pharmacovigilance system in which a toolbox approach can be used to identify, rapidly respond to, and communicate issues related to pharmacovigilance. The toolbox would contain "*a network of potential strategies that can be invoked at any one point in time.*" (National Pharmacovigilance Centre and Centre for Adverse Reactions Monitoring, Key Informant, February 2010)

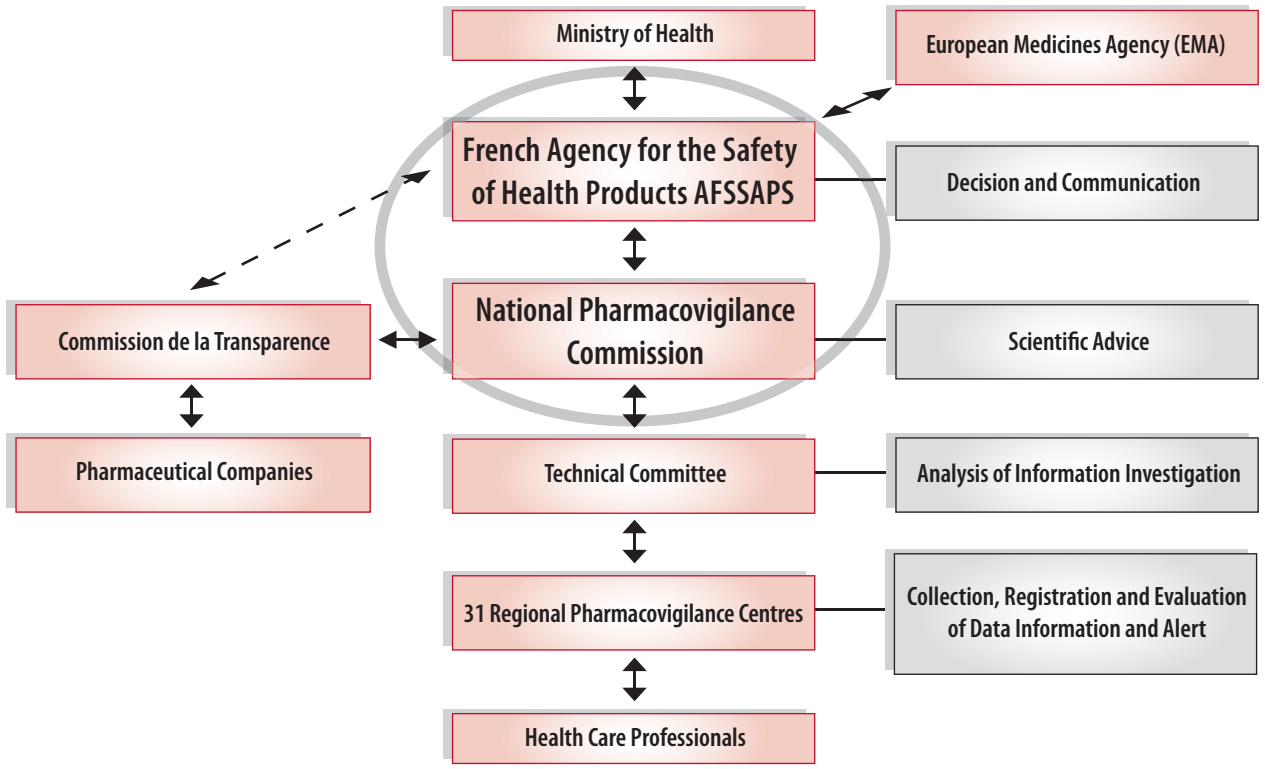
(E) France

In France, the National Pharmacovigilance Committee of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) undertakes prospective monitoring of particular drugs through one or more of its 31 Regional Pharmacovigilance Centres. For example, the AFSSaPS National Pharmacovigilance Committee commissioned a prospective post-market observational study to detect rare but severe or unexpected adverse effects associated with the Prevenar™ (pneumococcal) vaccine.[90] Regular monthly meetings of the Technical Pharmacovigilance Committee, composed of directors of the Regional Pharmacovigilance Centres, determine whether a potential ADR merits study; if deemed in need of further study, the matter is referred to the National Pharmacovigilance Commission, which considers whether to involve the regional centres in a follow-up survey. (Figure 5) However, in some cases there can be long delays before products are withdrawn from the French market.

Between 1998 and 2009, about 30 cases of pulmonary arterial hypertension and cardiac valve disease associated with benfluorex[r] (an appetite suppressant) were reported.

[r] Benfluorex is not sold in Canada or the United States.

FIGURE 5: PHARMACOVIGILANCE SYSTEM IN FRANCE



Similar drugs had already been removed from the French market, but instead of doing the same with this product, the National Pharmacovigilance Committee initially proposed "to await the results of planned and ongoing studies." The product was removed from the market at the end of November 2009.[91]

In France, ADR reports are collected through a combination of voluntary and mandatory reporting schemes. These reports are assessed for causality by Regional Pharmacovigilance Centre experts and drug company representatives using criteria developed in joint meetings, referred to as consensus conferences.[91, 92] To clarify the causal link, the experts may make suggestions for subsequent actions, such as product "challenge, de- and re-challenge,"[s] to the professionals who have reported the adverse drug reaction. Regional centre directors hold monthly meetings to discuss potential signals and decide which ones to assess further through formal or informal surveys. After an initial assessment of causality, the ADRs and their causality score are incorporated into the national pharmacovigilance database at the AFSSaPS.[92]

In France, the company proposes a risk management plan and specifies the tools it will use to minimize risks (usually for drugs approved through the EMA centralized system) as part of its application for market authorization. The proposed risk management plan can include information for patients and physicians and close follow up of patients. The Regional Pharmacovigilance Centres coordinate and implement the risk management plans. One centre is designated the *rapporteur* and carries out the risk management plan studies. Such studies are observational, which limits the conclusions that can be drawn from their results, and there is a concern that physicians will tire of the extra work of filling out forms for the growing number of risk management plans and may not participate. (Haute Autorité de Santè, Key Informant, August 2007).

[s] In a *challenge, de-challenge and re-challenge* procedure, a product suspected of causing a reaction is administered to a patient. If a reaction is observed, the product is withdrawn to see if the reaction disappears. If that happens then the product is administered a second time to see if the reaction occurs again.

The Regional Centres also have direct links to specialist clinicians, and this facilitates the implementation of prospective observational studies. The National Pharmacovigilance Commission, composed of health care authority representatives, pharmacologists, physicians, pharmacists and an industry representative, reviews the study results and recommends measures to the AFSSaPS to prevent or reduce ADRs. These measures include changing a product's approved use, disseminating information to physicians, reconsidering a drug's risk:benefit ratio, or recommending its withdrawal.[92] Although France does not have linked administrative population health care databases, a current project involves following a 500,000 population sample for 20 years, linking ADR survey results to electronic health care record information including data on hospitalizations and dispensed prescriptions.

The formation of the *Comité de liaison*—a joint committee composed of the regulatory agency, the network of Regional Pharmacovigilance Centres, and the Transparency Commission, which oversees listing of products on the public formulary—is an initiative designed to increase collaboration on studies of drugs once they are on the market and listed on the national drug formulary. A benefit of such collaboration is that there is less duplication in the studies requested by the regulatory and drug-reimbursement agencies. However, market authorization holders' oversight of the post-market and post-national formulary listing studies remains a limitation. (Haute Autorité de Santè, Key Informant, August 2007)

(F) International Approaches to Involve Research Networks in Active Pharmacovigilance

Regulators in the jurisdictions discussed above recognize the limitations of voluntary ADR reporting and regulatory systems have evolved to better support active pharmacovigilance, assess real world experience, and inform public decision-making on the safety and effectiveness of medicines. A comparison of the approaches adopted serves to highlight their strengths and weaknesses and can inform future best practices. A framework with the following variables serves as the basis for this comparison (public funding, research standards, transparency of the process, anticipatory or reactive decision-making process, involvement of the regulatory agency and public drug reimbursement scheme, the resolution (or not) of legal issues related to data access, data ownership, and data re-analysis.) Table 3 summarizes the experience of the five international jurisdictions and Canada with respect to these variables.

Table 3 has been updated. Click here to view the revised table.

TABLE 3: ACTIVE PHARMACOVIGILANCE AND RESEARCH NETWORKS: A COMPARISON OF INTERNATIONAL POST-AUTHORIZATION CONTEXTS

PHARMACOVIGILANCE RESEARCH	UNITED STATES	UNITED KINGDOM	FRANCE	NEW ZEALAND	EUROPEAN UNION	CANADA[t]
Public funding	High	Moderate	None	Low	Low	High
Research standards & independence	Yes	No	No	Yes	Yes	N/A
Transparent process	Yes	No	No	Yes	No	N/A
Decision-making process	Reactive/ Anticipatory	Reactive	Anticipatory	Anticipatory	Reactive	Reactive/ Anticipatory
Public reimbursement plans involved	Moderate (federal agencies)	Moderate: through NICE	High: Transparency Commission	Low	Low	N/A
Regulatory agency involved	High	High	High	High	High	N/A
Legal data access issues resolved	Process in place to resolve	Yes (GPRD)	Yes	Yes	No	N/A
Data ownership	Public	Regulator MHRA	Industry	Public	Public	N/A
Data re-analysis	Yes	No	No	No	No	No

LEGEND

Public funding:

High – a high level of publicly-funded research (public funding of $10 million or more annually)

Moderate – a moderate level of publicly-funded research; industry also funds much research (public funding of $1–10 million per year annually)

Low – limited publicly-funded research; most research funded by industry (public funding of less than $1 million annually)

None – all research funded by industry

Research standards & independance:

Yes – research guidelines and standards must be adhered to

No – specific guidelines are not developed; each study is negotiated with market authorization holder

Transparent process:

Yes – study design and objectives are publicly accessible

No – study design and objectives are not necessarily publicly accessible

Decision-making process:

Anticipatory – actively monitors and is informed by signals before drug products cause widespread problems

Reactive – commissions studies only after widespread problems occur

Public reimbursement plans involved:

Extent to which public reimbursement plans are involved in determining the products to be evaluated: low, moderate, high

Regulatory agency involved:

Extent to which the regulatory agency is involved in determining the products to be evaluated: low, moderate, high

Legal data access issues resolved:

Whether legal issues concerning the security of data and researchers' access to them have been resolved: yes; no

Data ownership:

Public, Regulator, Industry

Data re-analysis:

Yes – requests market authorization holder's raw clinical trial data and regularly re-analyses it.

No – requests summary data; does not regularly analyse market authorization holder's raw clinical trial data.

[t] N/A = Not available because many of these variables cannot be assessed in Canada because the Canadian process is under development.

SECTION 3: ISSUES AND IMPLICATIONS FOR CANADA

The following discussion outlines a series of pharmacovigilance issues with respect to specific implications for Canada.

(1) What's wrong with current systems for identifying problems with drugs that are already on the market and what new approaches are being developed?

All the international regulators surveyed in the development of this discussion paper recognize the limitations of voluntary reporting of adverse drug reactions (ADRs). Research shows that this passive reporting system captures only between 1% and 10% of ADRs. In addition to low rates of ADR reporting, another problem with this passive system of surveillance is that the total number of patients taking a medication is, in many countries, not known.

In the US, reports sent directly to the FDA from health care professionals and consumers account for only 5% of all ADR reports to the FDA (the remaining 95% are submitted by the pharmaceutical industry).

> *Reports are made to the FDA's MedWatch program, which is "designed to give the public a single portal of entry . . . [but] we do not do routine follow up on every report that we receive. We are not resourced for that. We do follow up on reports that are received when we believe further follow-up may inform our understanding of a safety issue we're evaluating."* (FDA Key Informant, March 2010)

New Zealand has one of the highest rates of spontaneous ADR reporting in the world, yet ADR reporting remains inadequate to effectively detect safety signals,[93] While France makes it mandatory for health professionals to report a suspected ADR,[92] the rate of under-reporting is similar to other countries.[35] If a health professional suspects that a serious or unexpected event is potentially related to a drug, she/he must report the event, regardless of whether she/he prescribed the medication[92] France does not currently permit ADR reporting by patients, but a pilot study is underway to determine the feasibility of patient reporting and to develop patient tools (e.g. reporting forms and a user guide). Since 2007, 200 patient ADR reports have been received.[94]

As a result of these issues, regulators are developing new approaches to engage in *active* pharmacovigilance methods. The mandate, public funding, and framework and infrastructure needed to support post-market research have only begun to be developed. The current emphasis is on (1) developing relationships with academic research centres with epidemiologic expertise and (2) facilitating experts' access to health care and drug benefit plan administrative databases, in order to gather real-world safety information to study and amplify safety signals related to marketed products. One such initiative is the FDA's Sentinel System that is being designed to augment the signals generated by ADR reports through the analysis of large health care databases. These databases will potentially provide an indication of both the number of patients taking a specific medication (denominator), and the subset that develops an ADR (numerator). Safeguards for anonymity and security of data must be adopted when health care databases are used for purposes other than direct patient care.

Another approach that can enable a better understanding of emergent safety concerns associated with a drug is to have regulators require drug sponsors to conduct and complete post-market safety studies. A post-market study may be a condition of the risk management plan or required when it is determined that ADR reporting is insufficient to establish risk.

Implications for Canada: The creation of the DSEN and Health Canada's intention to introduce a progressive licensing framework represent important steps towards a more active system of pharmacovigilance, although some important conditions (outlined below) will have to be met for these initiatives to be effective.

(2) What are the key issues concerning funding of post marketing drug safety studies?

Although regulators are increasingly aware of the need for pharmacovigilance strategies and post-market drug safety studies, pharmacovigilance remains underfunded. Current funding models include public and private options for commissioned research. Until very recently, publicly-sponsored real-world research was not conducted and publicly-sponsored strategies remain underfunded.

Relying on industry to oversee post-market drug safety studies introduces serious limitations because of the inherent conflict of interest. Pharmaceutical companies have been shown to report their pre-approval research selectively by publishing only clinical trials with positive results, or by publishing those with negative results in a way that conveys a positive outcome. One recent study found that published results made it appear that 94% of the trials conducted for 12 antidepressants were positive; however a FDA analysis of the same data found only 51% were positive.[76]

> *"I mean there's lots of evidence that manufacturer-produced information is biased.… But then we rely overwhelmingly on manufacturer's information anyway in all these decisions."*
> (NICE Key Informant, February 2010)

This issue emphasizes the need for public funding and oversight to ensure that post-market studies address key research questions, are designed to produce valid results, and are accurately reported.

> *"I think it's a good thing that we know that the FDA can potentially audit any of the studies related to drug safety, which helps us to really focus extra hard on getting things right. And that is helpful."*
> (DECIDE Key Informant, March 2010)

In the EU, the US, the UK, New Zealand, and France, regulator-commissioned drug safety and effectiveness studies from academic research networks avoid research bias and conflicts of interest, increase transparency, assure open access to research data, and enhance public perception of the validity of research findings.

The US offers the highest level of public spending in absolute dollar amounts to support active pharmacovigilance. The FDAAA assigned significant financial resources to support it in establishing the Sentinel System. Sentinel allows the FDA to gain access to information about the post-market safety of approved products by gathering real-world safety information from organizations that have agreed to participate. It is designed to complement ADR reporting by strengthening signals generated through queries of large health care databases.[79]

> *"… the vision is that we'll be able to go in and in an intelligent systematic way query large health care databases to see if we can essentially answer this question in a different way. Now I mean, Sentinel isn't being conceived of as another big spontaneous reporting source, but it's seen as a complement to spontaneous reporting to allow us to sort of further define things when we just have a small number of reports."*
> (FDA Key Informant, March 2010)

Like the EMA, the FDA does not commission clinical trials. However, independently and collaboratively with the AHRQ, the FDA commissions post-market observational studies, thus enabling it to contract academic research centres with access to health care databases to support epidemiologic research as issues arise.

In the UK, the MHRA allows academic research centres to work with it in developing funded research projects based on the General Practice Research Database. In addition, the Medical Research Council supports research projects recommended by the NICE. Various health agencies support disease registries.

In New Zealand, Medsafe works collaboratively with the Pharmacovigilance Centre to prioritize and publicly fund studies, but very few projects are actually funded. On the other hand, in the EU, drug sponsors themselves fund the post-authorization safety studies that are required as part of the sponsor's risk management plan. Although ENCePP has developed an inventory of academic research centres, industry will be responsible for funding the research. This is also the case in France.

The EMA believes that although it will not be funding ENCePP studies, the code of conduct and guidelines for research that it is establishing will ensure the evaluations produced are rigorous and protected from bias. The EMA itself provides only a modest amount of funding for post-market safety studies; the amount is insufficient to fund clinical trials.

> *"Well, I mean… if there's a market authorization holder for a particular product which is the subject of the study, then normally they would fund the study. ...We've established a small …EMA fund…about €200,000 per year to fund safety studies."*
> (EMA Key Informant, March 2010)

This EMA fund is targeted to address urgent safety issues because, according to our EMA key informant, the European Community public procurement process is slow and does not permit the EMA to respond rapidly to emerging issues. When such an issue arises, the EMA sends the call to a short list of pre-qualified centres:

> "*…we've chosen to set up a short list of qualified centres that will be valid for three years and when we have an urgent safety issue we don't need to publish the call for tender… but we can send the call to centres on our shortlist. …This procedure only covers up to €125,000. If we wanted to go above that we would have to follow a different procurement procedure.*"
> (EMA Key Informant, March 2010)

In addition, funding for the European Commission Framework Programme is not enough to support clinical trials:

> "*… the funding per project that the European Commission has does not normally cover clinical trials. It's in region of €3–5 million per project*[u] *and that over five years...*"[v]
> (EMA Key Informant, March 2010)

Reliance on industry funding continues despite conflicts of interest, research bias, publication bias, proprietary ownership of data, and other known issues. This trend is apparent in the EU, the UK, France and New Zealand. The EMA is attempting to address this through the ENCePP code of conduct and research guidelines intended to increase the rigour and independence of industry-funded research. In contrast, the FDA has begun to address this issue through enhanced funding of contracted, independent research, collaborating with partners that have access to health care databases, such as the VA, and by enhancing its own capacity to query health care databases through the Sentinel System. The *U.S. Patient Protection and Affordable Care Act 2010* earmarks funding for the development of a Patient-Centered Outcomes Research Institute to address gaps in the current pharmacovigilance strategy, particularly to support research on the comparative effectiveness of drugs.[87]

Implications for Canada: It is vital that Canada adequately fund a drug safety system that ensures that patient safety is protected. This will involve identifying the key areas in pharmacovigilance through a consultative process involving all of the key stakeholders. At the same time, it is necessary to ensure that money is responsibly utilized. One method of achieving this goal is through an independent monitoring function that will periodically look at the quality of the research and how well that research is translated into practices to enhance patient safety. Ongoing public funding is needed to: enable safety (pharmacovigilance) and effectiveness research that is free of research bias and conflicts of interest; assure open access to research data; increase transparency; and avoid the problems associated with industry concealment of unfavourable findings.

(3) How can capacity building for pharmacovigilance research be supported?

Lack of secure, ongoing funding was found to be a barrier to building a sustainable pool of experts in the area of drug safety research. Effective pharmacovigilance depends on a national commitment to build capacity and increase expertise in drug safety research. In jurisdictions such as the US a multi-pronged approach is used to build research capacity. This approach would generally include a national commitment to increase funding for graduate and postdoctoral fellowships, provide more support for early researchers, and increase funding for research infrastructure.

The newly passed US Health Bill, HR Bill 3590, provides a model for national policy that builds research capacity and provides sustainable funding for health outcomes and clinical effectiveness research on the risks and benefits of medicines. The legislation also supports the education of health care providers and researchers.

Implications for Canada: The federal government needs to commit to secure, stable and ongoing funding in order for the DSEN to be able to adequately plan and carry out long-term research. The CIHR should support graduate and postdoctoral fellowships in the area of pharmaco-epidemiology, provide more support for early researchers, and increase funding for research infrastructure to ensure that researchers with the necessary level of expertise are available to respond to requests for research proposals and are able to conduct investigator-initiated research in areas identified as priorities such as the advancement of research methodologies. There are implications for the DSEN as well: The DSEN must have the ability to fund priority research without jeopardizing ongoing studies. The network could serve as a national clearinghouse to train new researchers in a number of ways, for example through secondment from academia or government agencies and by sponsoring programs for postdoctoral

[u] The amount of money varies on a yearly basis. In 2007 and 2008 it was approximately €3 million and one project was funded each year, but in 2009 it rose to €12 million and 4 projects were funded.
[v] Depending on the number of patients enrolled, clinical trials could easily cost $50–100 million.

students. The DSEN should also help to ensure cooperation and coordination among the various research centres operating across Canada. Until a sufficient pool of expertise is developed in Canada, the DSEN will require ongoing support from the CIHR, the Social Sciences and Humanities Research Council, and the Natural Sciences and Engineering Research Council to increase research capacity and support the development of new methodologies.

(4) How can independent and rigorous post-market research best be ensured?

Public oversight is needed to ensure that drug sponsors and academic centres engaged in post-market studies adopt a rigorous research approach designed to produce valid results, with the independence that promotes accurate reporting. The EMA, the FDA and New Zealand's Medsafe are in the process of developing guidance documents for methodologic approaches that, if followed, will support rigorous research designs for epidemiologic studies to ensure validity and increase public confidence in research findings. The EMA's draft code of conduct should help to ensure that ENCePP studies are independent of commercial interests. The code for ENCePP-approved studies covers study protocol, data ownership and interim analyses and also requires registration of studies, publication of all findings (including a summary of prematurely terminated studies), development of protocols for access to raw and processed data, and declaration of conflict of interest by investigators, funders, or advisory group members. The code also requires academic centres to sign a declaration that rigorous methodological research standards will be followed that include a valid research design.[73] The EMA's member states, including France and the UK, have the ability to contribute to the guidelines and will have access to them.

All research networks expressed the importance of research independence, valid study design and rigorous research standards if network recommendations are to influence the regulator decision-making or affect the behaviour of health care providers and/or patients.

> *"But the important thing is that NICE tries to make sure that its science, whether it's clinical science or statistical or economic, is basically unchallengeable, not easily challenged. It's always been seen as being important that the minister could stand up in parliament and say this is what the best minds in Britain have had to say."* (NICE Key Informant, February 2010)

Advisory committees of the MHRA and the FDA are an important resource for research expertise. These expert advisory groups—composed of health professionals, epidemiologists, biostatisticians, consumer and patient representatives, toxicologists, risk communication and pharmacy systems specialists—offer recommendations on issues related to medicines.

The FDA collects data for independent analysis and audits studies commissioned from research centres. The FDA has adopted guidelines for industry-sponsored epidemiological studies and the Office of Surveillance and Epidemiology is developing guidance documents on how to use large administrative and other health care databases to answer drug safety questions. Public access to data produced by these research centres would enable auditing of commissioned research to assure quality.

Implications for Canada: Health Canada should draw upon best practices internationally in developing guidance for ensuring that research is independent and rigorous. All post- market medicines research that Health Canada requires from companies or that is publicly commissioned should be registered prior to commencement, avoid conflict of interest (as for example is specified in ENCePP's code of conduct), and be subject to guidance documents to ensure rigorous methodology is followed. Guidance documents for commissioned studies increase transparency in research. There are implications for the DSEN as well: The DSEN should develop guidance documents to ensure that commissioned research is carried out with appropriate methodological rigour, that conflicts of interest are avoided, and that all data coming out of commissioned research are publicly available.

(5) Why are certain drugs selected to be followed? How transparent is the decision-making process?

The decision-making process regarding the selection of the products to be studied in the post-market phase, and the type of study design that will be used to evaluate them, is not always transparent. Public oversight is needed to ensure drug sponsors and academic centres engaged in post-market studies adopt a rigorous research approach designed to produce valid results, with the independence that promotes accurate reporting. In the case of the EMA, the development of a risk management plan for market authorization and requirements for post-authorization safety studies can involve negotiation between the regulator and the product sponsor. However, although summaries of the risk management plan are publicly available, they often lack detail on the study design. In the US, industry representatives are non-voting members of FDA advisory committees, thus limiting conflicts of interest. The FDA's decision-making process is most transparent compared to other international regulators because advisory committee proceedings are publicly available.

In the UK, the NICE credits its strategy of including a wide range of stakeholders in decision-making for building public confidence in its findings and increasing acceptance of its technology assessments.

Implications for Canada: Broad stakeholder involvement should be incorporated in decision-making concerning publicly commissioned post-market studies. Such involvement will increase transparency, provide additional research expertise and ensure that consumer, caregiver, regulatory and health care funder perspectives are considered. At a minimum, all members on any committees set up by Health Canada to deal with safety issues must submit conflict of interest disclosures to which the public has access. Avoidance of conflicts, whenever possible, should be the ultimate objective. There are implications for the DSEN as well: The DSEN should have broad stakeholder involvement in the selection of areas to be studied and the methodology to be used. All members on any DSEN committee should be required to make fully public and detailed conflict of interest disclosures.

(6) When is the decision made to investigate a drug safety issue?

A decision to investigate a drug safety issue can be taken before there is any evidence for concern (anticipatory) or after a safety concern has arisen (reactive). New Zealand's regulator Medsafe and France's Transparency Commission, which oversees the listing of products on the public formulary, adopt an anticipatory approach; they request that studies be conducted for new products that are likely to have widespread use and represent a novel type of therapy at the time of market approval. Conversely, the approach taken in the US, the UK, the EU and Canada has typically been reactive, as regulators have responded only after a signal has arisen.[1] The experience of several products that have been withdrawn from the market, including rofecoxib (see Table 1 on page 11), suggests that although regulators were aware of certain safety signals, they failed to adopt an anticipatory or proactive approach to investigate. Rather, their response was reactive and delayed until after adverse effects produced significant and widespread harm. Regulatory response to emerging safety issues has been inconsistent. Regulatory authorities in many countries including Canada and the US issued warnings about the use of selective serotonin reuptake inhibitors (SSRIs) in youth with depression, suggesting a more proactive approach may be beginning to be adopted. On the other hand, insufficient warnings and communications regarding the risk of diabetes associated with atypical antipsychotic medications suggest the continuation of a reactive approach to safety signals.

Implications for Canada: If Canada adopts a progressive licensing framework and Health Canada gains the authority to require Phase IV (post-market) trials, and enforce compliance, a more anticipatory approach to drug safety will be possible. There are implications for the DSEN as well: While the DSEN and Health Canada should have a collaborative relationship that ensures sharing of information on emergent safety signals and risks of pharmaceutical products, the DSEN should have sufficient independence such that it can rapidly respond to safety signals and address issues requiring urgent attention. Similarly, it should have a mechanism to quickly commission research in these situations.

(7) What role should public drug plans and other public drug agencies play in pharmacovigilance strategies?

When public reimbursement schemes are involved in requesting post-market research, issues relating to the public's values, use of and interest in the medication must be incorporated.

> "*NICE realized quite early on that it isn't just the science that matters. And it conducted a similar sort of process involving people in order to produce—this, which is about the social values that are embodied within these processes.*" (NICE Key Informant, February 2010)

For example, a decision to provide access to new products is related to their associated risks and benefits as well as to economic considerations. Public citizen and public agency participation in the processes that help determine product use and adoption can help to guide decisions about which products to evaluate and how to evaluate them.

In addition to the values guiding decision-making, it may be wise to take into account specific real world considerations. For example, for a product that is intended to address a chronic condition, and thus must be taken over many years, the public drug benefit plan may be interested in assessing patients' compliance with the treatment. If patients have difficulty tolerating the medication, they may discontinue its use. Similarly, some products are approved on the basis of surrogate endpoints, and a drug plan would be interested in determining whether the treatment leads to a positive effect on long-term measures, such as a decrease in mortality.

In France, the Transparency Commission uses a tri-partite *Comité de liaison*, which coordinates requests for post-market studies between the national regulator, the drug reimbursement plan and the agency that sets drug prices. Although the NICE in the UK was established to review the evidentiary basis for listing products in the National Health Service formulary, the MHRA and the NICE do not necessarily coordinate post-market studies, and the EMA does not include public drug benefit plans in discussions concerning post-market safety studies. In contrast, the FDA and the VA have a memorandum of agreement to share information concerning pharmacovigilance in the US. The FDA has also established a Federal Partners Working Group to engage federal agencies involved in initiatives that are complementary to the Sentinel System that is being developed. Although this is a new initiative, it demonstrates the FDA's willingness to address the implications of how its decisions affect the public agencies, professionals and the population that will use the products it approves.

Implications for Canada: All provincial governments should adopt the approach that British Columbia has taken and collect data on all prescriptions filled in their respective provinces, irrespective of who the payer is. Provinces should adopt a common way of recording data to make it easy to access information on a national basis. This data should be quickly available to researchers at a reasonable cost. There are implications for the DSEN as well: The DSEN academic centres commissioned to conduct real world epidemiological studies on drug safety and effectiveness will require access to data from drug benefit plan prescription drug records and health care records, including access to disease registries.[w] In addition, the research centres should have access to data from the Common Drug Review, the Patented Medicine Prices Review Board, and other public and private organizations. This could be achieved through memoranda of understanding among the organizations involved. Data produced by research centres should also be made publicly accessible. This would enable auditing of commissioned research to assure quality.

(8) What is the appropriate role for regulatory agency involvement?

All national regulatory agencies and the EU's EMA are involved in determining the types of active post-market research studies that will be commissioned. Importantly, the regulators should have access to the companies' (market authorization holders') clinical trial data, on which regulatory decisions are based. Thus, the involvement of regulatory agencies is important to inform the types of post-market studies that would be of highest priority and the nature of the study design and, in research translation, to ensure that the results of completed studies inform their regulatory decision-making. Effective interagency governance and administrative structures must support regulators' ability to fulfill their mandate for pharmacovigilance. Cooperative decision-making models, equitable funding, adequate

[w] *Patient registries* are used to monitor whether the criteria for use of a particular product have been met and to examine the harm:benefit of a medicine, however since they are confined to patients who are already taking the product in question they lack a control group. *Disease registries* support more rigorous epidemiologic research than patient registries because they make it possible to design studies that categorize subjects into treatment and control group, enhancing the validity of the study.

staffing, and personnel development are essential in order to maximize pharmacovigilance activities. The U.S. Patient-Centered Outcomes Research Institute (PCORI) initiative in *HR Bill 3590* requires the PCORI to evaluate the effectiveness of the Institute's activities every five to eight years.

Implications for Canada: Health Canada, the DSEN and provinces and territories will have to work together closely to create an effective pharmacovigilance strategy that addresses public concerns. A model similar to that in the US should be adopted for monitoring and evaluating the effectiveness of Canadian initiatives to identify and respond to drug safety issues.

Compliance with post-market commitments is ensured when regulators have the legal authority to enforce study completion and can impose fines for failure to complete studies. Recent legislation gives EMA and FDA regulators powers of enforcement.

Before the passage of the FDAAA in 2007[77] a significant minority of market authorization holder commitments to conduct post-market studies were not fulfiled.[x] The FDAAA now gives the FDA the authority to impose penalties for failure to complete studies by the required deadlines.[14] (see Figure 1 on page 24)

Implications for Canada: Health Canada should be given additional authority in the area of post-market pharmacovigilance through the adoption of legislation similar to that in the US. There should be an ongoing assessment of pharmaceutical company compliance to complete Phase IV studies requested either as a condition of market authorization or in the form of post-market safety studies. Any fines that are imposed for failure to complete Phase IV trials must be significant enough to achieve their objective; fines that are too small will not have any value. In addition to fines, other options could be considered to ensure that Health Canada can enforce its requirements for post-market studies. These options could include a temporary ban on promotion or a temporary suspension of marketing authority. Finally, a list of all commitments required from industry should be made publicly available along with annual reports regarding the progress of these commitments.

(9) How effective is the communication of drug safety risks and of pharmacovigilance research?

Regulators in the countries researched for this paper have not placed a priority on evaluating the effectiveness of risk communication messaging and the regulatory actions undertaken to improve drug safety and reduce risk. No dedicated funding could be identified for assessing whether risk communication led to changes in prescribing behaviour or patient use of drugs.

The U.S. Patient-Centered Outcomes Research Institute (PCORI) initiative in *HR Bill 3590* includes the development of a protocol for dissemination of research results.

Implications for Canada: Health Canada should adopt a protocol for developing safety messages to be sent to provinces and other government agencies, health care practitioners and consumers. It should also adopt methods to monitor and evaluate message effectiveness and the effectiveness of Canadian initiatives to identify and respond to drug safety issues. There are implications for the DSEN as well: When the DSEN commissions research, it should require that completed studies include a plan for communicating results (knowledge transfer). The DSEN should also develop mechanisms to monitor changes in prescribing and drug use in response to dissemination of the research results.

(10) How should issues around data access, ownership, and use be addressed?

Regulatory agencies and research networks in all countries studied here report that they have limited access to data needed to conduct post-market safety studies. The data that are necessary to conduct epidemiological studies of the safety and effectiveness of medicines in real-world conditions are located in disparate sources, owned by entities that consider the information proprietary, and subject to regional variation in privacy laws.

One of the reasons publicly-funded research is needed is to ensure public access to the data. Regulatory agencies and academic centres commissioned to conduct research face problems because data on how pharmaceutical products are used under real world conditions can be proprietary and privately held by pharmaceutical companies, private

[x] Prior to the passage of FDAAA in 2007 there were a total of 1,531 post-market commitments and post-market requirements in a backlog; 15% (230) of those were delayed and another 30% (459) had no specific completion date or deadline associated with them.[95]

drug plans, provincial drug plans or regulatory bodies. As such, the data are not always accessible to researchers and may be costly to acquire. Even when data are publicly accessible, the cost may be prohibitive (DSRU Key Informant, July 2007); online access to the GPRD, including all data and selected data extraction tools, costs £127,500 a year.[y] Industry-funded research results are often considered proprietary, and public access is denied. The exception is the FDA, which makes public some of the data that sponsors submit as part of market applications.

For post-market studies, directors of drug benefit plans would benefit from a full understanding of the evidentiary basis for requiring such a study, as would consumers. As such, the ENCePP Code of Conduct specifies that the research centre conducting an industry-funded study is expected to have ownership of the data. In France and the UK, data in commissioned studies are owned by industry and data summaries are shared with the regulator and public drug benefit plans.

The FDA is the only regulatory agency that requires product sponsors to submit raw, unanalyzed clinical trial data, although other regulators, such as Health Canada, can ask for the data. Having data on hand is an important tool from the perspective of pharmacovigilance, as it gives a regulator the capacity to pool the data from separate clinical trials and thus increase the power to detect safety signals. A recent example of a safety signal detected through pooled data re-analysis was the adverse drug reaction of suicidal ideation associated with the use of SSRIs in teenagers. (DEciDE Key Informant, March 2010) As a result of this signal being identified, international regulators issued warnings against prescribing of antidepressants in teenagers. The pooling and re-analysis of data is clearly an important means to increase the power and strength of signals associated with adverse drug reactions.

National and international pharmacovigilance policy is supported by regulator involvement in setting priorities for research conducted by academic centres that have access to health care databases and adhere to established research codes of conduct.

For epidemiologic research that relies on access to patient information in health care databases, legislation must be in place to ensure the security and anonymity of such data when used for purposes other than direct patient care. Legal constraints could prevent research investigators from accessing or pooling epidemiologic data across nations and states. In Europe, the EMA encountered this issue when market authorization holders indicated they could not complete studies because they were unable to gain access to data due to legislative constraints. The FDA is currently engaged in a feasibility assessment through a review of the data privacy laws of the 50 states. In general, appropriate standards must be developed to safeguard the confidentiality of personal medical information in order to allow necessary research to be undertaken.

Implications for Canada: Health Canada has access to clinical trial data (that form the basis for deciding whether new drugs receive market authorization) and reports of adverse drug reactions through the voluntary ADR reporting system and the periodic drug safety reports that companies are required to submit on a regular basis. In order to generate hypotheses regarding potential safety signals with the objective of protecting public health, Health Canada should demonstrate the willingness to work in a synergistic manner with the DSEN and the researchers commissioned to conduct post-market studies. There are implications for the DSEN as well: The DSEN needs to develop memoranda of understanding with the relevant provincial and federal agencies in order to obtain access to data relevant to drug safety and effectiveness. In addition, the DSEN should negotiate for access to clinical safety, efficacy and effectiveness information owned by pharmaceutical companies.

[y] In the UK, NICE has attained access to clinical trial data through an agreement with the Association of the British Pharmaceutical Industry, which enables NICE to conduct its technology assessments. In this agreement, NICE had to agree it will not put "commercial-in-confidence" information it has obtained into the public domain prior to the product release date. The Drug Safety Research Unit in the UK holds an exclusive agreement with the National Health Services Business Service Authority for access to prescription data to conduct prescription event monitoring studies. In the US, the FDA has a Memorandum of Understanding with Veterans Affairs.

NEW INDICATIONS FOR THE USE OF "STATINS" SHOW HOW PHARMACOVIGILANCE SYSTEMS NEED TO BE ABLE TO RESPOND TO CHANGING CLINICAL SITUATIONS

The United States Food and Drug Administration (FDA) has approved the use of one of the existing lipid lowering drugs ("statins")—rosuvastatin (Crestor™)—for apparently healthy men and women who have normal cholesterol levels but high levels of C-reactive protein, a potential marker for the development of cardiovascular disease. This new indication for the drug will increase the number of people in the US who are candidates for lipid lowering medicines from 80 million to 86.5 million or by about 8%. The equivalent increase in Canada would be about 650,000 people.

This new group of people who are now eligible for treatment will be taking statins for primary prevention, i.e. to prevent the development of cardiovascular disease. A clinical trial involving participants with high levels of C-reactive protein found that the rate of major cardiovascular events was 1.36 per 100 person-years in those on placebo compared to 0.77 per 100 person-years in those taking rosuvastatin, meaning that 95 people would need to be treated for 2 years to avoid one event. Since the study lasted less than two years, the length of time is inadequate to determine long-term side effects.[96] The previous literature about the use of statins in primary prevention showed a decrease in deaths due to heart attacks and stroke (71 people would need to be treated for three to five years to prevent one death) but failed to demonstrate any difference in the overall mortality rate between those using placebo and those using statins.[97]

The degree of benefit from using the drug for this new indication will be key in determining the harm: benefit ratio. Benefits in this new population may be increased or decreased compared to the population currently using statins for primary prevention, but the harms associated with the drug will remain the same thereby altering the overall harm:benefit ratio.[98]

If Health Canada also expands the indications for rosuvastatin it would be prudent to investigate how the drug is being used in this new population to establish whether or not the same magnitude of harms and benefits seen in the randomized controlled trial are present in the real world. As is well known, efficacy and harms documented in clinical trials are not necessarily duplicated in the real world. The options for Health Canada would be a real-world clinical trial, a disease registry (difficult due to the large numbers of people who would be potentially eligible for such a registry) or a cohort study. Studies could be undertaken by the manufacturer, by Health Canada directly, or by a research network under contract to Health Canada, or through the Drug Safety and Effectiveness Network. Whatever option is chosen, cases such as this one illustrate the need for Health Canada to have an effective pharmacovigilance strategy capable of adapting to new situations.

CONCLUSION

Much remains unknown about the safety and effectiveness of medicines after they enter the market and large numbers of people start taking them. It is clear, however, that a passive system of monitoring drug safety—one that relies on voluntary reporting of adverse drug reactions—is not adequate to identify most emerging drug safety issues. As a result, regulators and drug safety experts around the world are developing systems to facilitate active surveillance of people's real world experience of prescription drug use in order to detect emerging safety concerns early.

In this discussion paper we have provided details of a variety of active surveillance strategies that are being developed and employed in the United States, the United Kingdom, France, New Zealand and the European Union.

In Canada, two of the key initiatives that have the potential to improve post-market drug safety through active surveillance are the recently established Drug Safety and Effectiveness Network (DSEN) and the proposed progressive licensing framework for pharmaceuticals that Health Canada intends to implement. However, as we note in the *Issues and Implications for Canada* section of our report, Heath Canada will need greater legislative authority if the new framework is to better protect Canadians, and the DSEN will require adequate funding if it is to produce independent, scientifically rigorous, and innovative research, and respond quickly to emerging issues.

To ensure public safety and the most effective use of prescription medicines Health Canada, the DSEN and the provinces and territories will have to work cooperatively. When used with appropriate safeguards to protect patient and provider confidentiality, provincial and territorial government health care and drug utilization databases will be a key resource for DSEN research, and provinces will stand to benefit from evidence that informs decisions about drug reimbursement policies.

It is our hope that this discussion paper, by providing insights and lessons based on international experiences with post-market surveillance of drugs, will help point the way for Canada to develop more responsive systems of research, regulation, and risk warning that lead to safer and more effective use of medications which in turn advance the health of the population and help to sustain our health care system.

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