Post-approval drug safety: moving from passive to active pharmacovigilance in Canada

Effy Koukoulas

Experimental Medicine - Biomedical Ethics Unit
McGill University, Montreal
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Abstract

Adverse drug reactions (ADRs) present heavy burdens for the public health care system, and current pharmacovigilance activities are challenged by the under-reporting of ADRs in spontaneous reporting systems and a lack of incentive for industry to conduct rigorous post-approval research. As part of a new lifecycle approach to drug regulation, Health Canada recently announced plans to develop a new health product vigilance framework that will allocate drug safety resources using prioritization schemes focused on higher risk. These plans include the development of official policy requirements for industry to submit formal Risk Management Plans to Health Canada. This thesis argues that this approach is limited by lack of transparency and standardization, burdens on health care practitioners, and a risk of causing treatment disparities.

This thesis presents alternative measures for improving post-market drug safety surveillance through initiatives for enhancing ADR data collection systems. These include the use of electronic health records for automated reporting by health care professionals, the screening of health-related social media sites for ADR reports, and the use of internet-based prescription monitoring systems to solicit ADR reports. This thesis also proposes options for improved post-approval research efforts. These include enhanced legislative authority for Health Canada to mandate post-market research commitments to drug sponsors as conditions of approval, offering extensions on data protection to sponsors in exchange for comparative effectiveness research, implementing mandatory industry-sourced funding for objective third-party research, and ensuring that the Drug Safety and Effectiveness Network contains adequate patient representation. In the current context of limited health care resources, these alternatives merit further consideration, including consultation and validation with relevant stakeholders, in order determine the most value-added methods for improving drug safety surveillance.

Résumé (*French Abstract*)

Les manifestations indésirables dues aux médicaments représentent une lourde charge pour le la santé publique d'autant plus que les activités actuelles de pharmacovigilance sont limitées, d'une part par le fait qu'un bon nombre de rapports spontanés ne sont pas comptabilisés dans les différentes bases de données et d'autre part parce qu'il n'existe pas suffisamment d'incitatifs pour encourager l'industrie à mener des recherches systématiques après qu'un médicament ait été approuvé. Dans le cadre d'une nouvelle approche de la réglementation des médicaments basée sur le cycle de vie de ceux-ci, Santé Canada a récemment annoncé son intention de développer un nouveau cadre sur la surveillance des produits de santé qui permettra d'allouer à l'innocuité des médicaments les ressources selon des priorités établies en fonction d'un risque plus élevé. Ce projet inclut le développement d'une politique officielle pour exiger de l'industrie qu'elle soumette des plans concrets de gestion du risque à Santé Canada. Ce mémoire soutient que cette approche contient des limitations causées par un manque de transparence et d'uniformisation, qu'elle représente un fardeau additionnel pour les professionnels de la santé et qu'elle risque de causer des disparités dans le traitement des données recueillies.

Ce mémoire présente des mesures alternatives visant à améliorer le suivi au sujet de l'innocuité des médicaments une fois que ces derniers sont sur le marché, en utilisant des initiatives visant à améliorer les systèmes de collection des rapports de manifestations indésirables. Ces mesures incluent l'utilisation de registres de santé informatisés pour les rapports automatisés provenant des professionnels de la santé, le criblage de sites Internet de type médias sociaux ayant un lien avec les rapports de manifestations indésirables et l'utilisation de systèmes de surveillance Internet pour solliciter les rapports de manifestations indésirables. Ce mémoire propose également diverses options pour l'amélioration des efforts de recherche une fois le médicament approuvé. Les propositions incluent une autorité législative plus grande pour Santé Canada pour inclure comme condition d'approbation des engagements fermes de la part des fabricants de médicaments d'effectuer de la recherche post-commercialisation, offrir aux

compagnies des extensions pour la protection de données en échange de recherche comparative sur l'efficacité, la mise en œuvre obligatoire de sources de financement provenant de l'industrie pour des recherches indépendantes effectuées par un tiers-parti et assurer que le Réseau sur l'innocuité et l'efficacité des médicaments contient une représentation adéquate des patients. Dans le contexte actuel où les ressources allouées au système de santé sont limitées, ces alternatives méritent qu'on s'y attarde davantage, et que l'on inclue la consultation et la validation avec les parties concernées, dans le but de déterminer les méthodes à plus grande valeur ajoutée pour l'amélioration de la surveillance de l'innocuité des médicaments.

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Chapter 1 – Introduction

Medications can be dangerous. They are developed with the objective of improving the health and well-being of patients, but they can inadvertently cause many detrimental effects. This can occur for a variety of reasons, including if a drug is not prescribed properly, if a drug is misused, if a drug causes unexpected side effects, and even if a drug simply doesn't work as intended.

Patients may have the misconception that marketed medications are safe since they have been approved by regulatory agencies. However, regulatory approval does not represent an absence of danger related to a medicine. What the public may not realize is that a drug's approval is actually very specific in nature; it designates a favorable risk-benefit profile for the drug only at very specific dosages, for the treatment of certain conditions in the exclusive populations that have been studied. What is problematic about this is that in the "real-world," the approved drug is used much more widely, in a broader range of patients and often even beyond its approved indication.

Because of the expanded use of a drug once it hits the market, no drug can be considered risk-free. This has led to popular expressions in the pharmaceutical industry regarding the need to establish the "right" drug for the "right" patient at the "right" dosage. This may sound more like branding rather than good science, and it may sometimes seem like pharmaceutical companies are looking for patients to match to their drugs rather than designing drugs to treat particular patient needs. Nonetheless, patients and pharmaceutical companies mutually benefit from having safe and effective drugs on the market, provided that there are adequate safeguards in place to ensure a continued, favorable risk-benefit ratio. In order to establish the right drug for the right patient at the right dosage, the safety and efficacy of a drug must be extensively studied and understood, and must be shared with health care professionals in a way that will help guide treatment decisions with their patients.

Monitoring the safety of a medication before and after regulatory approval is therefore critical for evaluating whether the benefits of a medicine continuously

outweigh its known risks. Pharmaceutical companies and regulatory agencies are charged with the legal and ethical responsibility of continuously reassessing the safety profile of approved drugs in order to ensure a favorable benefit-risk ratio. Despite ongoing methods for monitoring drug safety and effectiveness, adverse drug reactions (ADRs) continue to strain the public health care system, contributing to mounting evidence of a gap in current post-market pharmacovigilance efforts.

The objective of this thesis will be to identify the gaps in current pharmacovigilance activities in order to propose initiatives that will lead to more effective drug safety monitoring and improved public health. Subsequent chapters will analyze the limitations of spontaneous ADR reporting systems and phase IV studies as tools in the current regulatory framework for post-approval safety surveillance. This thesis will also explore the trend in regulatory modernization initiatives towards risk-based activities for drug safety monitoring, focusing on risk management plans, and will argue that these are not the most efficient use of valuable public funds as they do not maximize Health Canada's ability to protect patient health. Alternative methods for enhancing the collection of real-world safety and effectiveness data will be presented, including the use of electronic information technologies, incentives to perform well-designed, pragmatic post-marketing studies, and enhancements to third-party post-market safety and effectiveness research. The potential benefits and limitations of these proposals will be evaluated based on other similar, existing models for successful initiatives from Canada and abroad.

Background

According to various regulations and international guidance documents, the widely accepted, basic definition of an ADR is any undesired medical event in a patient receiving a medicinal product, involving a reasonable possibility of a causal relationship between the drug and the occurrence.[1 2 3] This definition extends to drug interactions, drug withdrawal symptoms, lack of drug efficacy, and drug exposure during lactation or during pregnancy (i.e. embryonic/fetal

exposure in utero, through the mother or exposure via semen). The scope of ADR reporting also includes medication errors and circumstances at risk of harming patients, even in the absence of an actual reaction, which is important since approximately 33% of medication errors are related to confusion regarding packaging or labeling of medication.[4]

Regulations also define the criteria for classifying ADRs as "serious" including, but not limited to, events that are immediately life-threatening or that result in death, events that require hospitalization or that prolong existing hospitalization, events that cause a persistent or significant disability, events that involve a congenital anomaly, and events that are judged medically significant when an intervention is required to prevent one of the aforementioned serious outcomes.

Prior to regulatory approval, investigational drugs are administered to clinical trial subjects in a controlled study setting. During clinical trials, study investigators are required to report to trial sponsors all adverse events experienced in trial subjects, regardless of causality.

The four phases of clinical trial development begin with an initial assessment of clinical pharmacology, usually in a small number of healthy subjects. These are phase I studies, and the primary objective is to collect data on safety, tolerability, pharmacokinetics and pharmacodynamics.[5] Similar pharmacological assessments are made in phase II studies, which are conducted in larger groups of patients with the target disease, in addition to testing preliminary efficacy, and correlating drug dose to therapeutic response.[5] Phase III studies are much larger trials conducted in the target population, usually via a blinded, randomized, controlled design.[5]

Phase IV studies are conducted after a drug's approval, with the objective of expanding the study population to include "real-world" circumstances, often focusing on ongoing safety surveillance activities.[5] Phase IV studies may be set up using a variety of designs and are often conducted as extensions of blinded, randomized phase III trials. These studies are commonly designed as observational ("non-interventional") trials, in which data are collected based on

routine clinical care, with drugs prescribed according to usual clinical practice and paid for by patients or insurers at a pharmacy, as in real life.

Although pre-licensure clinical testing may involve thousands of study subjects, some side effects are not observed during these trials. Due to the limited study duration and the restricted number and variability of study participants involved in pre-licensure trials, it is not possible to detect all potential adverse drug effects. This is especially true for very rare side effects that would not usually be observed in the limited study populations of clinical trials, and also for latent effects or those that only emerge after long-term therapy use. Since clinical studies tend to restrict the enrolment of subjects by recruiting only individuals who meet very specific inclusion criteria, study participants are not usually reflective of the "real-world" population. A wide variety of patients may be prescribed the drug once it has been marketed, with important characteristics that were not represented in the population of study participants, including the elderly, minors, patients taking many concomitant medications, patients with co-morbidities, etc. Unstudied factors in patients taking a medication once it has been marketed may lead to occurrences of unforeseen ADRs and a lack of drug efficacy, potentially posing dangerous risks for patients.

Exploring all of the potential patient variables in pre-approval trials that may later affect treatment decisions would be extremely challenging, due to the complexity of designing protocols to specifically seek out these relevant factors. Additionally, conducting such thorough trials prior to market authorization would cause significant delays in the drug approval process. This would not be ideal for patients waiting for new treatment options, nor for pharmaceutical companies, given the limited period of patent exclusivity (which begins when a drug is first discovered rather that when the drug is actually approved, usually 10-15 years later).

Population sample sizes in most industry-sponsored pre-licensure drug trials are designed to detect differences based on primary efficacy endpoints that drive regulatory approval rather than to detect adverse events.[6] The International Conference on Harmonization recommendations on sample sizes for studies with

certain medications (e.g., drugs intended for the long-term treatment of non life-threatening conditions) are insufficiently powered to detect effects that occur at a rate of one in 100 patients, let alone uncommon effects (frequency of 1/1000 to 1/100), rare effects (frequency from 1/1000 to 1/10,000) and very rare (frequency less than 1/10,000).[7]

Product labeling documents (such as the Product Monograph in Canada, the Package Insert in the United States, and the Summary of Product Characteristics in the European Union) document reported adverse effects, classified according to their reported frequency. Consequently, when these labels are approved by regulators at the time of licensure, they do not reflect the true risk of developing an adverse drug reaction, only the rate that was observed during clinical trials. Similarly, these drug labels do not predict the probability of success with the medication; rather, they summarize the efficacy rates from past clinical trial results. Since these labels are relied upon by prescribers and patients for guiding treatment decisions, this limited data set can be risky for newly approved drugs.

Post-approval surveillance activities have thus become increasingly important for monitoring the safety and effectiveness of therapeutic products following regulatory approval. While pharmaceutical companies often monitor medication safety through adverse event reporting in post-marketing surveillance studies, continued monitoring of drug safety is largely facilitated through the spontaneous reporting of ADRs experienced in patients receiving prescribed therapies.

In Canada, there is currently no legislation on mandatory reporting of adverse drug reactions by health care professionals to drug manufacturers or to Health Canada. However, pharmaceutical companies are required by law to document and analyze all adverse events reported to any of their employees, from any source, regardless of causality.[8] In Canada, drug manufacturers are required to report serious ADRs that occurred in Canada and serious, unexpected ADRs that occurred in other countries, to local health authorities within 15 calendar days. Additionally, drug companies must prepare annual summary reports for

each of their marketed drugs and must include analyses of all reported ADRs and any significant changes in the risk-benefit profile of their drugs.[8]

The reporting and analyzing of suspected ADRs through spontaneous reporting systems contribute to the detection of signals that could represent a potential safety concern related to a drug. This acts as a trigger for further investigation of a possible association between a drug and a reaction. Potential side effects that have yet to be confirmed can thus be potentially identified even earlier via spontaneous reporting mechanisms, which may contribute to the prevention of adverse effects in susceptible patients.

The Burden of ADRs and the Need for Enhanced Drug Surveillance

Canadians spent about $31 billion on medications in 2010, and as of 2011, there were approximately 13,000 drugs on the Canadian market, many of which are critical to quality patient care.[9] However, an alarmingly high incidence of ADRs is burdening health care systems; a 2008 study of Canadian hospitals found that 12% of emergency room visits were caused by drug-related AEs, 68% of which were considered preventable.[10] In the United States, an estimated 99,628 emergency hospitalizations each year among the elderly are caused by ADRs (approximately 1.5% of all emergency hospitalizations), primarily due to commonly used anti-thrombotic and anti-diabetic drugs.[11] Other studies have estimated that 5-25% of all hospital admissions are drug-related.[12 13] Studies have shown these rates to be generally consistent in other parts of the developed world.[14 15] In addition to these figures is the significant number of events that are more difficult to track because they do not result in hospitalization or because they occur in patients who are already hospitalized.[16]

The treatment of ADRs imposes a heavy economic strain on health care systems. For example, it has been shown that each hospitalization due to warfarin-related bleeding events has a mean cost of $10,819 in the United States.[17] Since there are estimated to be 21,010 hospitalizations in the United States for warfarin-related haemorrhages each year, the cost for this single type of

ADR is substantial. Given that public health care budgets are limited and that available resources are already significantly stretched, the impact of ADRs on health care expenditures is quite burdensome.[11] Beyond the cost of treating ADRs is the impact on the actual victims, who are inconvenienced by ADRs in many ways, even if they are not hospitalized (e.g., stress and suffering, time taken away from work and personal responsibilities, consultation with various HCPs, seeking alternative treatment options, etc.).

From 1969 to 2002, 75 drugs were removed from the US market due to safety-related issues and 11 drugs were granted special prescribing requirements and controlled distribution.[18] A study of drug approvals in the US from 1975-1999 found that 8.2% acquired a new black box warning and 2.9% were withdrawn from the market.[19] Analyses in this study estimated the probability of a drug acquiring a new black box warning or being withdrawn from the market over 25 years to be 20%.

Over the past decade, high profile media coverage related to various drug safety issues has heightened awareness of the risks associated with medication use. Examples of these issues include class-action lawsuits related to ADRs and extreme market actions taken with commonly used medications. One of the most notorious examples of this was the 2004 voluntary market withdrawal of rofecoxib (Vioxx), a non-steroidal anti-inflammatory drug, following results showing an increased risk of myocardial infarction, which confirmed the manufacturer's previous knowledge of this risk from a study conducted in 2000.[20] Another example is the controversy over rosiglitazone (Avandia), an anti-glycemic medication, that was found to be associated with an increased risk of serious cardiovascular events in 2007,[21] which was further demonstrated in data published in 2010.[22] These latter findings led to the market withdrawal of rosiglitazone in Europe and public warnings for restricted use in the United States and Canada.[23 24 25]

Issues like these can be very frightening for patients and may make them question why these drugs were ever approved in the first place. These concerns have given rise to demands for greater regulatory oversight, increased

accountability and transparency, and enhanced stakeholder involvement in the area of drug safety surveillance.[26]

Another factor contributing to the need for improvements in regulatory pharmacovigilance initiatives is the increasingly global nature of the pharmaceutical industry. Multi-national drug companies face a broad range of regulatory environments as they deal with local legislations in the markets where their drugs are approved. Industry groups have thus been seeking greater harmonization in the regulatory requirements related to drug approval and post-market safety surveillance. Additionally, globalization has led to the manufacturing and packaging of approved drugs in a variety of foreign countries, creating challenges for regulatory authorities to monitor the applied consistency of safety standards to imported medications. Globalization trends are also influencing patients, who are increasingly aware of the availability and pricing of medications in other countries and are often willing to access these medications from abroad, either through online pharmacies or via medical tourism. This further increases the need for regulatory alignment with other countries in the area of drug safety standards and surveillance.

In addition, evolving demographic trends in patient populations, including aging and immigration rates, have impacted disease patterns and prevalence of health risk factors. This has further increased the need for new treatment options, in addition to ongoing surveillance of existing therapies for chronic health conditions.[26] Patient advocacy groups are demanding faster access to new and innovative medications from their regulators and therefore expect health authorities to make important approval decisions about medications more efficiently.[27]

In response to these issues, many regulatory agencies, including Health Canada, the Food and Drug Administration, and the European Medicines Agency, are examining their role in post-approval drug surveillance activities, with an overall objective of improving patient safety. This has resulted in a variety of regulatory modernization initiatives by these agencies, as they seek to update their pharmacovigilance framework in order to enhance the oversight of marketed

drugs. The following chapter will critically examine the tools currently used for post-approval safety surveillance in Canada.

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Chapter 2 – Gaps in Current Pharmacovigilance Activities

Introduction

The Institute of Medicine considers public health agencies to have ethical obligations to protect the public from unsafe drugs.[1] Health Canada's legislative mandate with respect to medications is to ensure that the benefits of using a drug outweigh its risks.[2] This requires extensive pharmacovigilance activities and the timely communication of safety findings with stakeholders.[3 4] Regulatory pharmacovigilance involves assessing and monitoring the safety and effectiveness of marketed drugs, working with the pharmaceutical industry to provide accurate and up-to-date safety information, and implementing measures to reduce risks when needed. This is achieved by collecting and assessing safety and effectiveness data from a variety of sources, primarily consisting of adverse drug reaction (ADR) reports submitted by the pharmaceutical industry, health care professionals (HCPs) and patients or their caregivers, and from post-approval drug studies.[1]

This chapter will explore current practices for drug safety surveillance, with a focus on the generation of safety data from spontaneous adverse event (AE) reporting systems and from post-marketing clinical studies. This analysis will highlight some of the key limitations and ethical issues of these activities, including the under-reporting of ADRs by HCPs and problematic phase IV studies. This chapter will argue that spontaneous reporting systems and post-approval drug studies can be more effective methods for gathering relevant drug safety data if regulators address some of the their main limitations. This would help to ensure that pharmacovigilance activities are benefitting patients without burdening already stretched health care resources.

Background

Adverse event reports collected from various sources, including spontaneous reporting systems and phase IV studies, are entered into industry and

regulatory databases to undergo data mining activities. The objective is to detect safety signals in a drug, or within a class of drugs, in order to identify previously unobserved drug effects. Pharmaceutical companies and regulators track and analyze the frequency of reported AEs, and factors that may increase patient risk are evaluated in order to inform prescribers, so that the occurrence of ADRs can be minimized.[5]

The detection of safety signals from spontaneous reporting systems and phase IV clinical studies helps to shape medication labeling documents, such as the Product Monograph in Canada, through the addition of ADRs, contraindications, warnings, precautions, and notes for special populations (e.g., pregnant women, the elderly, and pediatric populations). Safety findings may also be disseminated through the scientific literature, regulatory newsletters, or ad-hoc letters to HCPs. They may give rise to risk management strategies, such as restricted drug distribution, and may even cause a drug to be removed or withdrawn from the market.

In order to monitor the risk-benefit profile of marketed medications, drug regulatory authorities around the world have ADR monitoring programs set up to collect and assess ADR reports for marketed products through signal detection activities. The United States Food and Drug Administration (FDA) uses its *Adverse Event Reporting System* database for documenting ADR reports submitted through its national MedWatch reporting program by consumers, HCPs or drug manufacturers.[6] Health Canada's post-market drug surveillance program is the Canada Vigilance Program, in which ADR reports are submitted to Health Canada's Marketed Health Products Directorate's *Canada Vigilance* database.[7]

Programs in different regions have varying operational features and reporting requirements[8] but are unified through a form of regulatory objectivity, in that they use conventions established through communication, coordination and standardization of the involved agencies.[9] This allows for consistency in the collection, analysis, and dissemination of safety information to enable international oversight of ADR data. For example, ADR reporting forms have common fields and guidelines for entering and classifying information, using

standardized definitions and terminology for coding and assessing case information.[10] This enables countries to participate in the World Health Organization (WHO) Programme for International Drug Monitoring, with at least 134 countries sharing information from national reporting systems.[3] These countries submit their ADR reports to the WHO database, contributing to signal generation for previously unrecognized ADRs and to the study of questions related to drug safety.[4]

Although the strength of spontaneous ADR reporting systems is the collection of real-world, near real-time data, from very broad population use, this is actually also one of the limitations of these systems. Due to the variability of patient responses to medications and confounding factors that may contribute to adverse symptoms, the detection of a true safety signal amidst the high volume of "cases" collected in AE reporting symptoms can be challenging. Additionally, some information is not easily accessible from spontaneous reporting systems, such as long-term drug effects, reliable comparisons between medications, and rare adverse effects associated with older drugs.[11 12] Furthermore, spontaneous ADR reporting systems are not designed to identify patient populations who are at greater risk or those who may be less commonly exposed to a medication. These factors are better studied through the systematic observation of defined populations in trial settings, using a variety of phase IV study designs.

Observational study methodologies are generally preferred for post-approval drug research, due to their ability to provide data based upon "real-world" conditions and because they generally provide more timely evidence than randomized controlled trials.[1] Observational study types may include the use of existing information from administrative databases or may be carried out using prospective cohort designs. However, the selection of study design may vary based on numerous factors regarding the drug, the patient population, and the nature of the scientific question to be addressed. Factors that may influence the selection of a post-approval study design include: the need to verify existing evidence of a shift in risk-benefit profile (e.g. based on the strength of a safety signal); the potential impact of confounders in the patient population; the

accessibility and quality of existing data; the possible need for an appropriate comparison group, and the associated burdens for study sponsors, clinician-investigators, and study participants (costs, logistical feasibility, availability of sample size, etc.).

Spontaneous ADR reporting systems

In Canada, pharmaceutical companies have legal obligations to document and analyze all AEs received by any company employee, and to submit reports of all serious ADRs within 15 days of initial awareness to Health Canada.[13] Strict company AE reporting policies and procedures are thus required to ensure compliance with regulatory reporting timelines. As such, industry employees are usually required to forward any AE reported to them (regardless of causality) for any of their company's products, from any source, to the company's pharmacovigilance department, within 24 hours of awareness. The case information is subsequently entered into the company's corporate safety database and each case is individually assessed with respect to seriousness and expectedness, as per the product's reference label. Cases involving serious, unexpected ADRs are distributed to affiliate offices in other countries, for submission to health authorities in jurisdictions where the company holds a license for the suspect drug and is required by law (as in Canada), to submit foreign reports to drug regulators.[14] Drug companies are also required to conduct routine data monitoring and signal detection activities and to submit aggregate reports of their analyses in accordance with Canadian regulations.[15]

One of the main constraints of spontaneous ADR reporting systems is that they don't represent the true ADR frequency in a given population taking a specific medication. The reported frequency of an ADR only reflects the reporting rate, rather than the actual incidence of the ADR in a population. Reporting can be inhibited and stimulated by numerous factors, which may limit the ability to detect new ADRs or to draw conclusions regarding a drug's causal role in an event.

The "under-reporting" of ADRs, calculated as the percentage of known, suspected or expected ADRs that were not reported by physicians to spontaneous reporting systems, is thus one of the main limitations of spontaneous reporting systems.[16] A systematic review of published data from 37 studies worldwide found the median under-reporting rate to be 94%.[16] In this review, no significant difference was found in the under-reporting rates between hospital physicians and general practitioners (GPs), however, in the EU, higher proportions of GPs reported ADRs in comparison to hospital specialists. Although there was a greater reporting rate for serious ADRs than for non-serious ADRs, there was considerable under-reporting of serious ADRs, including reactions that resulted in death.[16]

The ability of spontaneous reporting systems to identify new drug-related ADRs is firstly premised upon the accurate recognition of an event as being drug-related, and secondly, upon the adequate reporting of the case to a formal reporting system. Health care professionals are in the best position to detect and report ADRs, based upon observations from their daily medical practice, and are therefore a critical source of potential drug safety information.[2 17] By reporting ADRs, HCPs have the power to contribute to medical knowledge that shapes the evolving safety profile of medications. Indeed, a WHO study exploring the motivations in HCPs' decisions to report ADRs revealed that this decision was usually based on scientific motivation, especially for newly approved drugs, unexpected events, and severe events.[18] This motivation suggests that HCPs are aware that their ADR reports play a useful role in the risk-benefit evaluation of approved medications and that they indirectly enhance patient safety.

However, low ADR reporting rates are just as prevalent in countries where HCPs are legally obligated to report ADRs to regulatory agencies. For example, in Sweden, all serious ADRs, unexpected ADRs, and any ADRs that appear to increase in frequency must be reported to health authorities by HCPs.[19] However, a study exploring ADR reporting among physicians in northern Sweden found that over one third of physicians had never reported an ADR.[20] In this same

study, examination of 1349 patient records over a five year period revealed that 86% of documented ADRs had not been reported to regulators.

The first reason why physicians may not report ADRs is that patients often withhold this information, by not reporting all symptoms that they suspect to be ADRs to their physician.[21] This was observed in a study exploring suspected ADRs in patients in the UK receiving 'black triangle' drugs, classified by health authorities as requiring special surveillance efforts and the reporting of *all* ADRs by HCPs to the national spontaneous reporting system.[21] In this study, only 29% of patients indicated that they had reported all of their adverse symptoms to their physician.

There may be many reasons behind patients' decisions not to discuss all suspected adverse symptoms with their physician. Patients may not believe that they will be taken seriously[5] or their concerns may not feel as important once they are actually interacting with their physician.[22] In a qualitative study investigating whether patients' agendas are voiced during the clinical consultation, only 4 out of 35 patients actually expressed all of their concerns to their physician.[22] The most commonly unvoiced items included worrying about side effects and their symptoms, and not wanting a new prescription in relation to these factors. Unshared concerns were often associated with problematic outcomes, including the prescription of unwanted medications and subsequent nonadherence.[22]

Additionally, patients may not feel comfortable bringing up sensitive topics, such as sex-related symptoms, with their HCP. In a study on the use of antipsychotic drugs, the prevalence of drug-related sexual dysfunction was found to range from 25-60%, however, spontaneous reports of these side effects only accounted for 5% of the nationally reported ADRs in the treatment population.[23]

The second reason why physicians often underreport ADRs is a lack of engagement with patients' opinions regarding medications. Evidence suggests that during the clinical consultation, physicians do not routinely question or document patients' opinions regarding their medications, as this information is often not regarded as constituting conventional evidence in medical practice.[23] In the aforementioned UK study, only 22.6% of the adverse symptoms believed to

be drug-induced by patients were actually documented in patient records.[21] In this study, although 5033 reactions were experienced by 607 patients while using black triangle drugs, only 23 reports were submitted to the spontaneous reporting system.

In a 2007 study involving 650 patients taking statins who felt that they had experienced ADRs, most discussions about a possible connection between the drug and the reaction were initiated by patients rather than by physicians (98% versus 2% for cognitive reactions, 96% versus 4% for neuropathic reactions, and 86% versus 14% for muscular reactions).[24] Moreover, during these discussions, physicians tended to reject a causal link between possible ADR symptoms and the medication, even when a connection was strongly supported by the literature.[24] Given that physicians were inclined to dismiss reported ADRs, even when patients met presumptive criteria for a causal relationship to their medications, physicians may struggle even more with identifying rare or unexpected drug side effects.

A third reason for which physicians may not convey patient reports to drug companies or regulators is uncertainty regarding causality assessments.[20] During the patient consultation, clinicians apply their tacit knowledge as a means of dealing with uncertainty,[25] as in the assessment of medication as an underlying cause of newly presented adverse symptoms. This may include verifying if the drug was taken as prescribed, assessing a temporal association between the symptoms and the drug, reviewing the drug's safety profile (as per the product label and past clinical experience), and reviewing the patient's history for possible alternative causes.

However, the recognition and assessment of ADRs is challenged by the conventional course of decision-making by physicians, which is often driven by hypothesis-formation early in the process, with little inductive reasoning thereafter.[26] Tolerance levels for uncertainty among physicians may impact practice patterns, including quality of care for ambiguous conditions.[27] Confounding factors in a patient's medical history or concomitant medications that may also contribute to adverse symptoms may hinder successful recognition

and reporting of a drug's causal role in an AE. Determining causality can be especially difficult if drug side effects are difficult to distinguish from disease-related symptoms.

Physicians may thus be reluctant to report ADRs on the premise of suspicion, in the absence of confirmatory tests or other evidence. Nonetheless, the WHO urges HCPs to report clinically important, suspected ADRs as part of their professional responsibility, regardless of uncertainty regarding the role of the suspect drug.[17] However, when uncertainty is present, a busy HCP may be less willing to take time out of an overloaded schedule to report adverse symptoms.

Indeed, the fourth but most prevalent reason why physicians do not report ADRs is lack of time.[20] Locating and transcribing relevant information from a patient's chart (e.g., medical history, concomitant medications, dosing details, etc.) can be time-consuming: paper-based methods take an average of 36 minutes.[28] In today's strained health care system, devoting this much time to reporting ADRs is difficult to justify. Consequently, there is a need to facilitate ADR reporting for HCPs without creating additional burdens.

Phase IV Studies

Post-approval drug studies can identify serious health risks associated with approved drugs. These studies can prompt product label changes, including the addition of boxed warnings and contraindications, and may even lead to a drug's market withdrawal. Examples of major safety concerns identified in post-approval studies include the risk of sudden death with stimulants for attention deficit hyperactivity disorder, the risk of death in elderly patients with conventional antipsychotics, and the risk of myocardial infarction with COX-2 inhibitors.[1]

In industry-sponsored phase IV research, investigators are required to promptly report all serious AEs experienced by study participants, regardless of causality, to the sponsoring company who is responsible for subsequently submitting related cases to Health Canada.[13] However, the potential of post-

approval drug studies to generate useful safety information is currently limited due to a variety of factors.

Firstly, post-approval drug research suffers from variable implementation across industry due to lack of incentive. In Canada, there is generally no requirement for drug companies to conduct post-marketing studies. Once a drug is approved, Health Canada has little authority to mandate these studies, and phase IV protocols do not require a clinical trial application to Health Canada, since they are conducted within approved indications, and thus do not require regulatory review.[2] This may also contribute to the publication bias and incomplete reporting often associated with observational studies.[29–31]

Exceptionally, some drugs are granted conditional regulatory approval in the absence of substantial safety and efficacy evidence, with a commitment to conduct post-market research. However, these commitments are intended to complete the data set for these drug approvals rather than to generate real-world data, and there is no requirement for sponsors to provide regular updates on these conditions.[2]

In the US, the Food and Drug Administration Amendments Act (FDAAA) of 2007 granted the FDA the legislative authority to mandate post-approval research studies to drug companies. The FDA can now require drug sponsors to submit a timetable for the completion of the required study and for the submission of periodic progress reports, and can enforce these requirements through monetary penalties for companies that fail to comply.[32] Additionally, efforts to promote transparency, including enhanced authority to the FDA to enforce trial registration, have increased documentation of post-marketing studies on clinical trial registries.[2 33] Consequently, even though this authority is limited to studies performed specifically in response to post-marketing requirements, the FDA has greater oversight of phase IV studies than Health Canada. Absent local regulatory requirements to conduct post-approval drug studies, there is little incentive for drug companies in Canada to perform this type of research. These studies can be expensive and complicated to conduct and can be commercially risky for drug sponsors if the study results are unfavorable. This conflict of interest may

interfere with the decision to engage in post-market research or may negatively influence decisions regarding which kinds of studies to undertake.

Consequently, a second limitation of post-approval drug research is often poor study design. Two of the suggested minimal requirements for ensuring the ethicality of clinical research consist of value and scientific validity.[34] The requirement for validity consists of both internal validity (ability to exclude confounding causal factors) and external validity (generalizability of the results to other patient population settings or variations in treatment approach). Consequently, studies should be appropriately designed to adequately respond to the research objectives. This requires the application of sound scientific principles, including the use of an appropriate group of study participants and active comparators, as required.[35] In order for a study to be considered valuable, the objective should be to evaluate a hypothesis that will generate information that can potentially improve human health or well-being.[35] The research study should be designed to generate data in response to a novel question about a medicine that has not been previously answered.[36]

Value and validity can be compromised when phase IV studies are used as a vehicle for the promotion of newly approved medicines. This has been seen in seeding studies, which are clinical studies designed by drug companies to influence prescribing habits of targeted physicians, under the guise of scientific research.[36] The strategy behind these studies is to familiarize physician-investigators with newly approved medicines in order to increase the likelihood that they will prescribe these drugs outside of the trials. A further strategy is to involve key opinion leaders in these studies, in order to influence them to serve as spokespeople for new drugs and to apply pressure to government funding agencies to add these drugs to provincial reimbursement formularies.[37] Consequently, seeding trials are often accused of being unsystematic and superficial and of failing to provide any substantial safety data.[38] As a result, distrust in the scientific rigor and the clinical value of these studies has understandably given post-market research a bad reputation.[39]

Two of the most notorious seeding trials were the STEPS trial of gabapentin (Study of Titration to Effect Profile of Safety)[40] and the ADVANTAGE study of rofecoxib (Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness).[41] Evidence has demonstrated that these studies were primarily designed for promotional purposes, with critical responsibilities for both held by their sponsor's marketing division (e.g., hypothesis formulation, protocol design, investigator training, and data collection, analysis and dissemination).[37 42] Clinician-investigators involved in these studies were actively monitored for changes in their prescribing behavior, both during and after these studies, in order to determine if their participation led to increased prescriptions.[45]

The lack of scientific rigor in the design of phase IV studies intended for marketing purposes can give rise to study data with low value.[34] For example, in the STEPS trial, scientific rigor was undermined by poor quality data and a weak study design, limiting the generalizability of the study results and diminishing the value of this trial.[43]

The challenge in assessing the ethicality of post-marketing studies is that they tend to be minimally risky to study participants, especially in the case of observational studies and retrospective chart reviews. Although study participation may cause some anxiety, an enhanced placebo effect, an increased perceived sensitivity to AEs, and behavioral changes as a result of being observed (the Hawthorne Effect[44]), these risks are not much higher than for patients receiving a new sample drug from their HCP.

However, even though these studies are minimally risky to trial participants, they are unethical because they use up the valuable time of clinicians in exchange for little intended contribution to medical knowledge. Participation in post-approval research takes time and attention taken away from other initiatives, including more worthy research projects or activities related to patient care. Time commitments can be even higher for investigators in the absence of the experience and infrastructure needed to efficiently recruit patients, manage follow-up logistics, and maintain proper documentation.

Physicians recruited as investigators in the ADVANTAGE and STEPS studies were selected regardless of any experience in clinical research, because they were desired prescribers according to the sponsors' sales and marketing teams.[37 43] The ADVANTAGE trial involved 600 investigators and 5557 subjects[42] (averaging about 9 patients per site) and the STEPS trial involved 772 investigators and 2759 patients (averaging about 4 patients per site).[41] The number of patients per site for these trials was relatively low, considering that pivotal pre-licensure trials (which tend to much more thorough and labor-intensive) involve an average of 13 patients per trial site in Canada.[45] Although involving physicians without previous study experience may make sense in some phase IV studies (in order to collect "real-world" data)[44] the relatively low number of patients per site in STEPS and ADVANTAGE was more likely attributable to the intent to expose the drug to as many physicians as possible.

Given the shortage of physicians in Canada,[46] ensuring that approved research projects have scientific merit and are efficiently conducted is important for stewarding health care resources. The STEPS and ADVANTAGE studies would have been more efficient if they were instead conducted at a few large academic centers, specialized in performing clinical trials, with dedicated infrastructures and resources.[43]

While low patient-per-site recruiting targets may serve as an indicator suggestive of seeding studies to research ethics boards (REBs), suspected marketing motives alone do not make a study unethical. In theory, the intent of all pre-approval and post-approval studies for drug companies is to bring a profitable drug to market and to subsequently expand that market. Consequently, even if this information is available to REBs, it does not necessarily facilitate the evaluation process.

However, a third limitation of post-approval research is that it bears a tainted reputation from seeding studies that damage the institution of trust associated with the scientific research method. This breach of trust occurs at multiple levels, beginning with those directly involved in seeding studies or affected by their results and who may end up feeling understandably deceived.

On a deeper level, seeding studies compromise the system of medical knowledge production and the evidence-driven practices that rely on it. Interference with the generation of socially valuable medical knowledge in clinical studies compromises the integrity of the institution of scientific research, dissolving trust in the clinicians participating in these trials and in the companies that sponsor them.[47] Although phase IV studies pose few risks to participants, a lack of study value and/or validity threatens the system used for generating the medical knowledge that feeds into socially important evidence-based policies and practices.[48] This can have negative implications for stakeholders who rely on information produced from this system, including HCPs, policy-makers, and insurers, which can lead to sub-optimal or even harmful treatment selection for patients.[48]

Poorly designed phase IV trials thus threaten post-approval drug research by jeopardizing the credibility of the pharmaceutical industry and the system used for generating scientific information. This threatens the future collaboration needed for long-term knowledge production and potentially casts doubts upon "evidence" produced from subsequent industry-sponsored research initiatives.

Conclusion

This chapter has described the key limitations of spontaneous ADR reporting systems and has explored the ethical issues that arise when science takes a backseat to marketing in seeding studies. While post-approval studies and spontaneous reporting systems are important for collecting real-world data, their potential to contribute to the production of knowledge on drug safety and effectiveness is unmet as a result of these limitations.

Time constraints are one of the greatest challenges for HCPs in submitting ADR reports to spontaneous reporting systems. Consequently, in order to generate increased ADR data, there is a need to facilitate spontaneous reporting mechanisms or data collection systems.

Once a medication has been approved, drug companies generally have few incentives beyond marketing to conduct costly post-approval studies, and these studies can be difficult for REBs to assess because of their minimal risk to study participants. However, studies that are not well designed or geared towards producing valuable information are unethical because they drain resources that could otherwise be allocated to more worthy causes and because they threaten trust in scientific research as a means of producing useful medical knowledge. Consequently, there is a need to ensure that adequately designed post-approval drug studies are being performed to legitimately contribute to scientific information.

The following chapters will examine possible solutions for addressing the limitations of these activities, in addition to exploring alternative methods for enhancing drug safety surveillance.

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Chapter 3 – Risk Management Programs: Remedy or Red Tape?

Introduction

Regulatory reform is needed to address the current gaps in post-market drug safety surveillance. In an effort to improve drug safety monitoring, Health Canada is currently developing a new product vigilance framework that uses a risk-based approach to drug safety surveillance. This approach focuses on the prevention of safety problems, including adverse drug reactions (ADRs), with targeted oversight for higher risk medications, by prioritizing and enhancing surveillance measures for these drugs and allocating resources to them proportionately.[1]

The trend towards risk-based pharmacovigilance began in the European Union (EU) and in the United States (US), with new requirements for risk management programs (RMPs) from drug sponsors. Health Canada is also moving towards RMPs in its future model for drug approvals and has already begun to request that risk management plans be submitted by sponsors as part of new drug submissions, although this is not yet a standard component of the formal drug approval process.[2]

In theory, RMPs can be very beneficial as they are intended to help drug sponsors develop a proactive approach to risk management planning, in order to potentially minimize ADRs in patients. Additionally, RMPs may help to give patients accelerated access to new, efficacious medications that might otherwise not be approved due to specific safety concerns. However, in practice, RMPs are flawed because they are premised upon impracticalities for the agents responsible for their development and implementation.

This chapter will explore RMPs and their implications for drug sponsors and healthcare professionals (HCPs). This analysis will highlight the key limitations of RMPs, including their poorly defined expectations; the lack of transparency and standardization in their development; their burdens on HCPs; their questionable effectiveness in improving patient safety, and their risk of causing treatment disparities. This chapter will argue that the RMP policy being

implemented by Health Canada is suboptimal for improving patient safety and that Health Canada should instead consider alternative measures for enhancing drug safety surveillance.

Background

Over the past few decades, there have been multiple, high-profile cases of widely used medications found to cause serious harms in post-market studies. Among the most controversial of these drug scandals included the risk of cardiovascular events with rofecoxib and the risk of pediatric suicidality with paroxetine.[3] These cases highlighted the need for more effective measures to monitor drug risks in the post-market setting, in addition to the need for increased regulatory authority and oversight.

In the US, these controversies contributed to the development of the Food and Drug Administration Amendments Act (FDAAA) in 2007, which granted increased regulatory authority to the FDA over medications in post-approval safety monitoring.[4] The FDA now has the authority to mandate the submission of RMPs, entitled risk evaluation and mitigation strategies (REMS), as part of new drug applications submitted by drug sponsors. Factors considered by the FDA when determining if a REMS is needed include the novelty of the drug, the size of the treatment population, the seriousness of the indication, the duration of treatment, the expected drug benefits, and the known and potential ADR profile of the drug.[5]

The FDA is also authorized to require drug sponsors to submit a proposed REMS for drugs that were previously approved without a REMS, if new safety information identifies the need for a REMS to ensure that the drug's benefits outweigh the risks.[5] Failure to comply with REMS requirements can lead to penalties of $250,000 per violation, which can accrue to $10 million over time if the manufacturer continuously fails to address FDA notifications.[5]

The standard components of the US REMS include: a "Medication Guide," which contains the drug labelling document (the product package insert) and information for patients on safe and effective use; a "Communication Plan,"

which describes how HCPs will be informed of drug risks and REMS elements; "Elements to Assure Safe Use," which describes specific measures to mitigate serious risks; and a timetable for submission of assessments of the REMS, including methods by the sponsor to monitor the impact of the REMS on risks.[5] Not all products with REMS have all of these components, however as of August 2011, 49% of REMS involved more than one of them.[6]

In the EU, the European Medicines Agency (EMA) is responsible for ensuring that drug sponsors implement risk management activities as needed to effectively monitor and manage risks associated with their medications.[7] Risk management plans were introduced in the EU in 2005 as a means of minimizing known risks and monitoring potential risks, and must now be routinely submitted by pharmaceutical companies for all new drugs, as part of the standard drug approval process.[8] The EU risk management plan template consists of 3 main sections: firstly, a "Safety Specification" section describes the known safety information for the product, including known and potential risks, and areas of uncertainty or limitations in the clinical data set; secondly, a "Pharmacovigilance Plan" describes how the sponsor intends to collect further data to address areas of uncertainty; and thirdly, a "Risk Minimization Plan" describes how the sponsor intends to prevent or reduce the risk of ADRs.[9]

Although the format and content of the EU risk management plans and US REMS templates differ, the objective of these RMPs is to characterize the drug risks and to address the need for activities to minimize and monitor these risks. As in the US, an EU risk management plan may be required for already approved drugs, if emerging safety information warrants the establishment of strategies to ensure a favorable risk-benefit ratio.[5 7]

In Canada, the *Food and Drug Regulations* do not officially give Health Canada the authority to require a drug manufacturer to submit a RMP. However, in 2009, Health Canada formally announced its intention to implement RMPs as part of its new risk management strategy.[10] Accordingly, Health Canada has already begun requesting that RMPs be included in new drug submission applications, using the EU risk management plan template.[2 10 11] RMPs may be

specifically requested by Health Canada during "pre-submission meetings" held with drug companies to solicit feedback from regulatory reviewers regarding upcoming new drug submissions. If the sponsor's subsequent submission does not contain information requested at the pre-submission meeting, Health Canada has the authority to issue a Screening Deficiency Notice, requiring the missing information within specified timeframes or withdrawal of the application.[12] Consequently, as commonly seen with nonbinding recommendations in drug regulation that come to be followed as if they were compulsory, RMPs have become a reality for drug sponsors in Canada even though they do not have an official place in Canadian legislation. As a result, RMPs have begun to utilize resources at Health Canada, with reviewers responsible for evaluating submitted plans.[10] From 2009 to June 2012, Health Canada reviewed 191 RMPs, which did not include many RMPs submitted during that period but not yet reviewed.[13]

Pharmaceutical companies may use a variety of risk mitigation strategies in their RMPs, which range in complexity. The most common strategies involve the provision of educational materials to HCPs, such as medication guides, informative communications, and training courses on drug risks. As of October 2011, there were 199 active REMS in the US (before then, an additional 85 drugs were released from REMS requirements as the FDA felt that medication guides based on product labels no longer fall under RMPs).[5 14] Another requirement may be the need for HCPs to formally document their discussions on risks with their patients prior to prescribing a drug. HCPs may even need to sign a formal contract with patients, similar to the informed consent process in clinical trials, in order to acknowledge awareness of drug risks and to commit to specific measures needed to mitigate these risks. More elaborate RMP activities include registries used for collecting information on individual patients, and phase IV research and drug utilization studies to obtain outcomes data in the context of real-world drug usage.[5 15] The most onerous RMP systems for patients and HCPs involve dispensing requirements (such as patient testing to verify specific laboratory values before a drug is dispensed or administered) or restricted distribution to

HCPs who have received specific training or certification. As of August 2012, at least 25 drugs had REMS with requirements of this nature.[16]

Current Canadian legislation on RMPs does not include any formal provisions on penalties for HCPs who do not comply with RMP requirements. However, access to certain medications with RMPs may be withheld if certain RMP requirements are not fulfilled, as in the case of restricted distribution systems. For example, in preparation for a new class-wide opioid REMS in the US, federal agencies were working with Congress to create mandatory training requirements linked to the registration number needed to prescribe controlled drugs.[17] For medications with less stringent RMP activities, such as the distribution of medication guides to patients, the intent is to have HCPs fulfill these requirements, even though there is no way for drug sponsors or regulators to enforce these practices.

Challenges for Industry

The ability of RMPs to mitigate any risk is based upon the strategic design of the risk minimization interventions developed by drug manufacturers. However, the lack of regulatory guidance on RMP development and the conflict of interest for drug sponsors in designing RMPs for their own medications interfere with the success of RMP policy. Indeed, many of the challenges related to RMPs arise from the current lack of regulatory guidance and standardization regarding these programs, given the relatively recent nature of RMP policy. Drug companies contend that they are working diligently on RMPs but struggle with understanding: undefined criteria that trigger the need for an RMP; expectations regarding which measures to implement; and inconsistencies among individual Health Canada reviewers, with no apparent systematic assessment process.[2] Indeed, Health Canada's website acknowledges that "Health Canada's expectations regarding risk management activities and plans are not always clear to manufacturers, health professionals, or the public."[11]

Health Canada does not define its expectations for individual RMPs, nor does legislation empower Health Canada to formally negotiate submitted RMPs with sponsors. Given the lack of regulatory guidance on designing RMPs, drug sponsors are largely left to their own devices in determining which RMP strategies to select for their drug. However, manufacturers are inherently biased against risk management systems that could limit access to their medications. Additionally, their selection of risk management elements may be influenced by the costs and resources related to implementing and managing these programs. For example, certain risk minimization activities, such as restricted drug procurement systems and large-scale surveillance studies, can be very expensive, translating into higher costs for drug companies. In addition, RMP development within drug companies may require many internal resources, with input needed from a wide network of departments (e.g. pharmacovigilance, regulatory affairs, epidemiology, clinical research, etc.).[2] Consequently, with the rising number of RMPs requested by Health Canada, drug companies will increasingly evaluate whether certain risk minimization activities can be supported from a commercial perspective, based upon the anticipated post-market profits.

In Canada, the lack of regulatory guidance on the design and implementation of RMPs is exacerbated by the fact that unlike US REMS, risk management plans submitted to Health Canada are not publicly available. This is challenging for a number of reasons, including a lack of transparency to industry, patients, HCPs, and anyone else interested in learning more about drug-specific risk programs. This also creates a silo effect in the development of RMPs, leading to different safety standards for similar risks in different drugs, and creating disparities in risk minimization requirements for stakeholders. As a result, HCPs may have difficulty when trying to keep track of the responsibilities related to prescribing and dispensing drugs with RMPs.

As an initial step towards standardizing RMPs in the US, the FDA mandated the development of an industry-wide REMS covering extended-release and long-acting opioids in response to the widespread problem of prescription drug abuse in the US.[18] These drugs are commonly associated with overdose,

addiction, and death, because they are often mis-prescribed, misused, and abused, with more than half of opioid abusers obtaining opioid drugs from a friend or relative.[17] In response to the growing problem of prescription drug abuse, all brand name and generic manufacturers of opioids in the US were required to work together to create a joint class-wide REMS document for all extended-release and long-acting opioids.[17]

Prescription drug abuse is also a prevalent problem in Canada, which ranks as one of the world's top per capita consumers of opioids.[19] In Canada, prescription opioids have become the predominant form of illicit drug use by street drug users, with a substantial amount originating from the medical system, through family or friends.[19] However, unlike the FDA, Health Canada is not taking a standardized RMP approach across all opioids, instead requesting that risk minimization strategies be customized on a case by case basis to address problems with individual products.[20] This lack of harmonization and transparency creates uncertainty for drug sponsors regarding the standards for risk mitigation strategies to be used and makes it challenging for HCPs to keep track of responsibilities associated with different opioids.

Another challenge for drug manufacturers is the evaluation of RMP effectiveness. RMPs must specify the criteria to be used to verify the success of proposed risk minimization activities. However there is currently no model for how this success should be measured, nor have any RMP interventions been validated as effective methods for reducing harm to patients.[7 9] Consequently, there may be many different approaches to evaluating the effectiveness of an implemented measure. For example, if a RMP proposes developing educational materials to reduce the risk of medication errors, a sponsor may choose to verify the success of this intervention by administering knowledge-testing surveys to patients and HCPs. Alternatively, the effectiveness of this intervention may be verified through patient outcomes, using mechanisms for tracking specific endpoints, such as ADRs or medication error rates. Accordingly, the results of different evaluations for the same intervention may vary, and sponsors are likely to gravitate towards designing these assessments so that they are expected to yield

favourable results. As a result, most stakeholders, including drug companies, HCPs, and insurers, generally agree that it is virtually impossible to measure the benefits and cost-effectiveness of REMS for newly approved drugs.[21]

Of course, it is likely that in due time, based on accumulated experience, Health Canada will be able to provide greater clarity to sponsors by defining their expectations for RMPs, even if these are simply modeled from the FDA or EMA guidance. However, while this clarity may be useful for drug companies when drafting their RMPs, it will not address other far-reaching challenges associated with the use of RMPs. In a recent US survey of patient advocates, drug sponsors, HCPs and insurers, only 22% of respondents thought that the FDA REMS program is an improvement of the FDA's existing system.[21] About three quarters of the respondents felt that this system needed to be revamped and 68% felt that it was a poor substitute for other possible system-wide improvements, including enhanced drug education, communication, patient monitoring, patient access, and delivery of care.[21] The more problematic issues associated with RMPs are related to their implementation, rather than their development, as RMPs impose burdens on the HCPs responsible for delivering their interventions.

Challenges for HCPs

Most of the commonly used strategies in RMPs are generally targeted at HCPs, including the provision of medication guides, communication plans, training courses, patient testing, certification programs, and registry maintenance. Consequently, RMPs indirectly designate HCPs as the agents responsible for delivering drug safety interventions designed by drug sponsors to patients. The logical reason for targeting HCPs in risk minimization interventions is likely their proximity to patients. However, this strategy is based upon the premise that HCPs have the professional interest, in addition to the material and cognitive resources, to actually carry out RMP requirements, which is a problematic assumption.

In reality, RMPs interfere with the exercise of medical professionalism, which is especially evident in certain medical subspecialties, including oncology,

medical genetics (e.g. orphan diseases), and infectious diseases (e.g. HIV). These fields involve a collaborative, cross-functional network of highly specialized HCPs, closely involved in the care of individual patients. As a result of this expertise, *de facto* safety standards are generally already established in order to minimize drug risks, whenever possible. This can be seen in the systems of double-checks by pharmacists and nurses when dispensing and administering chemotherapy, to verify clinical appropriateness and to monitor laboratory values and clinical signs and symptoms for toxicity.[22] In these subspecialties, the role of RMPs is questionable and therefore undermines the professional authority of HCPs and hampers with routine clinical practice.

When faced with the possibility of prescribing a drug that has RMP requirements for HCPs, clinicians generally have three different options: *1)* to prescribe the drug and to fulfill the associated RMP requirements; *2)* to avoid prescribing the drug because of the RMP requirements; or *3)* to simply prescribe the drug just as they're used to doing, without following applicable RMP requirements (when possible).

RMP policy presumes an ability and willingness by HCPs to readily participate in RMPs, and is premised upon the notion that HCPs will choose *option one*, prescribing the drug and fulfilling the associated RMP activities. However, in reality, resource constraints pose one of the greatest challenges for HCPs in their ability to support RMP activities.

Hospitals and other medical centers often lack the expertise and resources needed to meet mandatory RMP requirements, such as components of restricted distribution systems, including staff certification and registry maintenance.[23] In Canada, there is still widespread debate regarding the adoption of electronic health record tracking systems. Additionally, there is no consistent information management system among those who have accepted administrative databases at various points of care, including hospitals, clinics, pharmacies, and private practices.[24] Consequently, many HCPs lack the basic technical requirements needed to follow RMP commitments. In the absence of infrastructures needed to support the administrative burdens of RMPs, stretched resources will become

further strained by the workload associated with prescribing drugs with RMP requirements.

Although oncology drugs have a disproportionate number of complex REMS requirements, access to these drugs is often critical for patients, so HCPs in these fields may feel more inclined to choose *option one*.[22] However, in the context of today's overburdened healthcare system, this choice can have negative implications for HCPs. In a study of oncology HCPs by the National Comprehensive Cancer Network (NCCN) in the US, 37% of participants were spending between 1 and 4 hours per week meeting REMS requirements, 5% were spending 4 to 8 hours per week, and 4% were spending more than 8 hours per week on fulfilling these responsibilities.[22] Even RMPs that involve the relatively simple requirement to distribute medication guides can be burdensome; systems must be implemented for tracking which drugs have these requirements, maintaining supplies of up-to-date guides, and ensuring that guides are dispensed with initial prescriptions, in addition to refills, as needed.

HCPs generally feel that the lack of financial incentives is resulting in low participation in RMP activities, and that if a specific patient education component is required, HCPs should be compensated for their time in delivering the material.[23] Since there is no monetary compensation for these activities, healthcare centers end up bearing the costs of RMP requirements and devoting additional time to administrative tasks, including document management and logistical planning. Given the growing number of drugs with RMPs, the seemingly benign administrative duties associated with tracking and fulfilling RMP requirements can quickly add up. A 2004 study exploring stress levels from job strain and risk of burnout among 2810 Canadian physicians found that administrative duties contribute to daily distress associated with practicing medicine and that physicians with administrative responsibilities have the highest levels of distress.[25]

There is little research on the effects of RMPs on quality of care; however, in a survey of over 2000 pharmacists conducted after the 2007 FDAAA implementation, approximately 60% of respondents reported that their daily

practices were negatively impacted by RMPs due to excessive costs and confusing procedures.[26] Since then, pharmacy groups have argued that REMS requirements cause problematic workflow implications and that they can be very confusing, creating a risk of increased medical errors.[27]

Furthermore, there is mounting pressure for HCPs to deliver more efficient care in order to minimize healthcare costs. As per the most recent American College of Physicians Ethics Manual, physicians are responsible for using healthcare resources efficiently, in order to ensure that resources are equitably available.[28] Moreover, physicians are being increasingly charged with the responsibility of initiating the redesign of cost-saving measures.[29] Consequently, *option one* is impractical for HCPs, since the allocation of finite healthcare resources towards RMP-related tasks will inevitably compromise other patient care activities. Indeed, the NCCN study found that 55% of HCPs felt that REMS will interfere with patient care, reporting that the administrative burdens reduce the time allotted for patient care and that REMS requirements occasionally ignore the obvious expertise of providers and institutions.[22]

The added burden associated with RMPs for certain drugs may deter HCPs from prescribing these medications altogether, choosing instead to prescribe other drugs without any RMP constraints (*option two*). This can be problematic for patients as it may lead to suboptimal treatment selection. For example, Tysabri (natalizumab) and Rituxan (rituximab) are two different drugs widely used for the treatment of multiple sclerosis, and are both known to increase the risk of progressive multifocal leukoencephalopathy, an often fatal brain infection.[30–32] Rituxan does not have a RMP, but natalizumab has a restricted distribution system that requires HCPs to be enrolled and trained in the TOUCH (TYSABRI Outreach Unified Commitment to Health) program in order to be authorized to prescribe, dispense and administer it.[33] From a regulatory perspective, this discrepancy is likely related to the fact that multiple sclerosis is an off-label indication for rituximab versus an approved indication for natalizumab.[30 31] Consequently, the context of the risk-benefit assessment for rituximab is different and may not warrant an RMP, and even if it did, REMS must be based on a drug's approved

label.[5] This is problematic for three reasons: Firstly, this means that drug manufacturers are unable to provide risk information to HCPs for off-label medication use, even if this use is widespread and considered appropriate based on available evidence (although this is an issue that extends beyond RMPs).[22] Secondly, since rituximab and natalizumab are used for the same condition, these different safety standards can be confusing and misleading to patients. Thirdly, since rituximab is much easier to prescribe, there is a potential for increased off-label prescriptions. A similar concern was voiced in the NCCN study, in which 60% of participants felt that RMP requirements will drive use toward drugs without REMS.[22] Additionally, almost one quarter of participants admitted being unwilling to prescribe/administer a drug with RMP requirements (instead opting for alternatives with equivalent effectiveness and toxicity, or referring patients to another HCP willing to follow applicable REMS).[22] However, there does not yet appear to be any evidence to substantiate any alterations in prescriber practices or any impact on patient outcomes.

Similarly, in a survey of 259 physicians regarding the upcoming opioid RMP in the US, only 50% were willing to comply with the mandatory education imposed by REMS (including prescriber training and the requirement to provide education to patients).[34] In this survey, 13.4% of physicians said that they will discontinue prescribing an opioid if required to complete 4-8 hours of training; 18.3% if required to enroll patients in a registry; 12.2% if required to deliver mandatory patient education; and 10.4% if required to document ongoing patient monitoring.[34] Of course, since this survey was performed prior to the finalization of the opioid REMS, the responses in these hypothetical questions may not reflect how physicians will actually react when faced with these scenarios in the real world. However, if physicians do choose to avoid prescribing long-acting opioids, this will likely lead to increased prescriptions for short-acting opioids, which are out of scope for the new REMS. This would likely decrease the quality of life for patients who require treatment with long-acting opioids for effective, sustained pain control, such as patients suffering from cancer-related pain. Additionally, the new opioid REMS does not fully address issues related to opioid

drug abuse, as street drug users will still be able to access short-acting opioids illicitly.[18] This REMS may even give rise to a "black market" for long-acting opioids, with drug abusers and legitimate patients both trying to obtain these opioids through illicit sources. Since the opioid REMS was only recently approved (in July 2012) the actual impact of the new REMS requirements on HCPs and on patient care is still unknown.[18]

However, given the burdens associated with *options one* and *two*, HCPs may consider *option three*, to simply prescribe medications as they're used to doing, without following any applicable RMP procedures. Of course, this is not possible for drugs with mandatory RMP activities that are prerequisite to treatment access. Yet, even for drugs with "non-mandatory" interventions, such as documentation of risk discussions with patients or distribution of medication guides, this may not be a popular choice as HCPs will likely still feel obligated to comply.

Despite the absence of regulatory enforcement or professionally justified standards for following RMPs, clinicians are likely to feel compelled to meet RMP requirements since physicians in the US, Canada, and the UK are thought to be motivated by a fear of malpractice liability.[35] This stems from many factors, including lack of awareness of legal standards, sensationalized media reports of exceptional lawsuits, and the deliberative authority of a tribunal of laypersons.[35 36] This fear of litigation has resulted in the widely reported concept of defensive medicine, whereby physicians are prone to adopting excessive precautions to reduce the risk of malpractice liability and its associated threats (stress, defamation, time away from practice, etc.).[35 37]

For claims of medical negligence, the Supreme Court of Canada defines the scope of the duty of fiduciary professionals based on medical judgment of a variety of patient factors, and determined in court on the basis of expert medical evidence.[38] Given the lack of evidence to support RMP requirements, refusal to carry out RMP activities would unlikely constitute a failure in due diligence and would likely not result in increased liability exposure. However, given the fear of malpractice claims, RMPs create an increased level of perceived professional risk

for HCPs, regardless of any formal enforcement policies, making non-compliance with RMP activities an unfavourable option. Consequently, HCPs are more likely to comply with RMPs, as per *option one*, (or avoid drugs with RMPs altogether, as per *option two*), and to manage the associated consequences.

Given the lack of available evidence to demonstrate the effectiveness of RMPs for improving patient safety, the added workload burden associated with widespread RMP use is difficult to justify in the context of improved standards of care.[6] HCPs therefore understandably feel that the benefits of RMPs must be weighed against their associated costs and burdens, and that RMPs should only be used when they are absolutely critical for ensuring patient safety.[39]

Conclusion

Although some elements of RMPs may be beneficial in certain situations, these programs can have negative implications for their stakeholders, making them ineffective as widespread, long-term strategies for improved public health. This chapter has explained that RMPs suffer from a lack of regulatory guidance, place excessive strain on healthcare systems, and create barriers for HCPs that may limit access to medications for patients who legitimately need them. Given the lack of evidence on the role of RMPs in improving patient safety outcomes and on their cost-effectiveness with respect to healthcare expenditures, the burdens of RMPs are difficult to justify. In the context of these realities, RMPs appear to be sub-optimal tools for reducing drug harms to patients.

Any further development of RMP policy should be suspended, pending a thorough examination of the implications for stakeholders and an assessment of the actual effectiveness of RMPs. Furthermore, since RMPs are designed in relation to specific known or anticipated safety concerns, and are generally not intended to detect or prevent unexpected safety issues, RMP policy will not eliminate the need for more robust surveillance systems designed for areas of safety unaddressed through RMPs.[39] Consequently, a more efficient use of limited public funds at the regulatory level would be to focus on initiatives that

can bring greater value to drug safety surveillance, as will be presented in the following chapter.

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Chapter 4 – Practical Approaches to Active Pharmacovigilance

Introduction

In order to improve drug regulation, Health Canada is planning to implement a progressive licensing framework, characterized by the ongoing re-evaluation of drug benefits and risks, based on information collected throughout a drug's lifecycle.[1] This lifecycle approach is also highly endorsed by the Institute of Medicine, which was called upon by the FDA to evaluate how to address drug safety concerns in the post-market setting.[2] Although progressive licensing has been widely discussed since it was presented by Health Canada in 2006,[3] there has been little implementation of any concrete steps to adopt a lifecycle approach to drug regulation. In September 2012, Health Canada presented its new product vigilance framework, which highlighted its responsibility for the regulatory oversight of the drug industry and the development, implementation and enforcement of necessary legislation.[1] In order to fulfill its mandate, Health Canada is interested in adopting more effective and efficient surveillance practices, including proactive vigilance methods to complement current passive surveillance.

The early identification of adverse drug reaction (ADR) signals and timely regulatory action are critical to the lifecycle approach. However, current post-approval drug surveillance mechanisms are limited in their ability to quickly generate information needed for signal detection, largely due to under-reporting of ADRs in passive reporting systems and the lack of well-designed, phase IV studies. Health Canada is ultimately responsible for ensuring that the benefits of a drug outweigh the risks,[4] and should thus be utilizing the best means of monitoring drug effects in order to collect information about the safety of approved medications.

As per the previous chapter, risk management programs (RMPs) are less than optimal measures for enhancing drug safety. Consequently, alternative mechanisms for collecting drug safety information merit consideration in order to detect new drug-related concerns more effectively and efficiently. The

implementation of these measures will require a shift from passive surveillance to active drug safety and effectiveness monitoring.

This chapter will propose measures for addressing the limitations of current passive drug safety systems. These consist of: 1) enhanced HCP reporting systems using electronic technologies; 2) enhanced patient reporting systems, including the use of various online methodologies for collecting ADRs; and 3) initiatives that promote post-approval drug studies, including requirements and incentives for conducting pragmatic trials, and enhancements to third-party post-approval research. This chapter will explore the benefits and limitations of these proposals and will defend against possible objections, such as data quality and signal detection concerns, patient privacy, funding, and conflicts of interest. Existing models and successful pilot projects on similar health-related initiatives will be used to support the feasibility of these proposals as alternative methods to RMPs for post-approval drug safety monitoring.

1. HCP Reporting Systems: Electronic reporting mechanisms

The recent increased prevalence of electronic health records in Canada[5] provides an opportunity for a new mechanism for reporting ADRs directly from the point of care. This can potentially occur via automated electronic submission by HCPs, using digitized data and information technology. This option is worth considering as Health Canada has announced an interest in adopting new and emerging value-added technologies and data sources.[1] Additionally, $2.1 billion have been invested in *Canada Health Infoway*, an independent, federally-funded, non-profit organization, commissioned to accelerate the development of electronic health information systems across Canada.[6]

In a recent collaboration between public and private partners, a new web-based method for reporting ADRs to the FDA using electronic health records was piloted in a project entitled "Adverse Drug Events Spontaneous Triggered Event Reporting" (ASTER).[7] The ASTER system was designed to prompt the creation of an ADR report whenever a HCP indicated in a patient's electronic chart that a

drug was discontinued due to a suspected ADR. The system automatically populated an ADR report form with relevant patient information (e.g. demographics, vital signs, medication, etc.), requiring little input from the HCP other than an opportunity to validate the data and to enter the ADR onset date and outcome.[7] The ASTER system was found to significantly increase the efficiency of submitting ADR reports, automatically generating reports that would otherwise require 36 minutes to prepare using traditional reporting methods.[8] As a result of this facilitated reporting system, participating clinicians who had generally submitted no ADR reports in the previous year ended up submitting 217 reports to the FDA over 5 months through ASTER.[7]

ASTER represents an important initial step towards improving the quantity and quality of ADR reports using digitized patient charts. Overall, the main limitations of this model were consistent with those of traditional spontaneous reporting systems and were not specific to electronically-triggered reports.[9]

As with any other spontaneous reporting mechanism, implemented electronic reporting systems like ASTER will need to have safeguards in place to protect the privacy of patients and HCPs. This is important as misuse of personal information can have many negative consequences, including identity fraud or discrimination due to health status. Canadian legislation requires that organizations have policies and procedures implemented to protect personal information and to ensure that it is only used for the purpose that it was collected.[10] Consequently, drug companies must already have confidentiality measures in place to protect private information collected for pharmacovigilance activities, so there is a minimal risk of this information being used to the detriment of an identifiable patient. Alternatively, collected information can be anonymized using a variety of algorithms for de-identifying data to ensure that the risk of identifying an individual patient is acceptable under applicable legislative standards, while preserving the utility of the data set.[10 11]

As for the quality of the reports received from ASTER, the FDA considered this automated reporting model to be a potentially valuable source of

information, pending a few enhancements in the design of the electronic chart to improve the quality and utility of the reports in pharmacovigilance activities.[9] Since the value of any ADR reporting system depends on the quality and relevance of the data it provides,[8] the usefulness of automated electronic reporting systems will be directly affected by the design features of the health record templates being used.

The potential of automated reporting systems may also be limited by the absence of a consistent information management system at various points of care within provinces and territories across Canada (i.e., hospitals, clinics, pharmacies, private practices, etc.).[5 6] Furthermore, there is still widespread debate regarding the benefits of adopting electronic medical records in clinical practice and therefore some reluctance towards accepting them.[5] However, given the substantial financial investment in electronic records and the need to strengthen drug safety surveillance without further burdening HCPs, this is a practical and timely solution for medical centers that are adopting these systems. Given the ongoing electronic record expansion efforts across Canada, this is an opportune time for Health Canada to provide input towards defining the design of these records so that they are conducive to automated ADR reporting.

2. Patient Reporting Systems

2a) Limitations and Opportunities

HCPs have traditionally been the gatekeepers to information on ADRs.[12] However, another solution for addressing the under-reporting of ADRs is to implement systems that increase the volume of reports from patients and their caregivers. Although Health Canada already accepts ADR reports sourced from patients, regulations in the EU only require drug companies to report ADRs received from HCPs (or patient reports that were subsequently medically confirmed by their HCP).[13] However, as of 2004, over half of the EU member states were actually receiving ADR reports from consumers through their own spontaneous reporting systems, handling them locally in the same manner as those

received from HCPs.[14] Increased reporting by patients and acceptance of these reports by regulators may potentially help to address the issue of under-reporting. However, an analysis of the potential benefits and challenges of processing patient-sourced reports is needed prior to considering proposals for increasing the volume of these cases in drug surveillance initiatives.

Patient associations have become increasingly powerful in the popularization of medical knowledge, promoting information as the key to enabling patients to question treatment options and to participate in decision-making.[15 16] The evolution of the doctor-patient relationship has led to increased patient involvement in their own care, combining their personal values, perspectives and preferences with the expertise of their physicians to evaluate treatment options.[17] As a result, lay groups have become increasingly involved in sharing scientific information, especially through the internet, including online forums, such as the Association of Cancer Online Resources.[18] The public availability of educational resources and social media tools has facilitated the exchange of scientific information, providing patients with new access to knowledge on diseases and treatments, including information on ADRs. Patient support sites are not only used for emotional support purposes; they often contain detailed medical accounts of patients' health, including experiences with various medications and drug side effects. A study exploring ADR awareness among patients found that at least half of the participants became aware of information on drug side-effects through various popular media sources.[19]

Patient groups are also increasingly involved in the production of medical knowledge. This is exemplified in popular epidemiology, a community-oriented approach to traditional epidemiology, focusing on the social context of links to disease.[20] The ability of lay groups to contribute to the generation of ADR knowledge was illustrated by the International Myeloma Foundation (IMF), a patient advocacy group that investigated osteonecrosis of the jaw in patients with multiple myeloma. Through online discussion forums, IMF patients discovered a possible link between this rare, disfiguring disease and zoledronic acid (Zometa), a treatment given to multiple myeloma patients. Using an online patient survey,

the IMF subsequently concluded that zoledronic acid was causing osteonecrosis of the jaw, which led to an update in the drug's label.[21] Given this new model of patients engaging in the production of evidence, each patient's unique illness experience qualifies them to make a potential contribution to the production of medical knowledge.[16]

Consequently, the quality of ADR reports should not be conflated with the quality of clinical judgment, in that a lack of medical expertise should not necessarily be viewed as a limitation to reporting an ADR.[22] A study exploring the cognitive model used by patients for recognizing side effects found that patients are able to draw upon a preconceived awareness of ADRs as a framework for recognizing that they may be experiencing a drug-related event, enabling them to interpret, assess, label, and report their symptoms accordingly.[19] In general, ADR reports from patients are similar in quality to those reported by HCPs and concerns regarding low quality reports from patients appear to be unfounded.[23]

Proponents of patient ADR reporting point out that these reports tend to contain richer details regarding the sequence of events leading up to ADRs, the emotional and social impact of ADRs, and their effects on quality of life.[23] Conversely, when an ADR is suspected during a clinical consultation, the patient's narrative is reconstructed by the physician using medical judgment, and inferences to evaluate the relevance of patient information are made to establish a framework for the shaping of a clinical case.[24 25] As a result, ADR reports made by HCPs embody a highly selective and often depersonalized representation of patients. While the filtering of details by HCPs can be important for efficiently managing patient care, the omission of certain contextual information may lessen the usefulness of ADR reports. For example, in a study that compared the value of ADR reports submitted for paroxetine by patients and HCPs, reports from patients were found to contain useful information and insights that were not provided by HCPs.[26] Patient reports were much more descriptive in communicating information on behavioral effects, suicidality, and withdrawal symptoms, providing important insights into the significance and consequences of ADRs in a personal and social context.[20]

However, while this detailed information may be useful for contributing to a collective, comprehensive representation of the dimensions of ADRs in specific treatment populations, the usefulness of this information is limited in the evaluation of a drug's overall risk-benefit profile. Detailed patient information is drowned out during signal detection activities, which are generally based on aggregated, coded medical terms and outcomes, with little, if any, focus on indvidual patient accounts. Furthermore, since patients tend to be less precise in their use of medical terminology, ADR reports received from patients are more difficult to classify and analyze according to international coding systems and may thus take longer to process.[27] For example, in the previously cited paroxetine study, reports submitted by patients were found to be deficient with respect to technical and medical terminology.[26] Additionally, the lack of medical evidence provided by patients may make causality assessments by drug companies and regulators challenging, especially since patients may take multiple concomitant medications and have other confounding conditions. Consequently, increased resources may be needed in order to process a higher volume of patient-sourced reports.

Another concern about patient ADR reports is whether they are able to provide reliable information, given a patient's limited ability to assess causal attribution of adverse symptoms. Some studies investigating the validity of ADR reports made by patients in various spontaneous reporting systems have found these reports to contain reliable information in relation to specific drugs.[28–30] However, further research is needed to support their use in pharmacovigilance activities that are based on an increased volume of patient reports.

The lack of expertise needed to distinguish drug-induced events from disease-related symptoms understandably gives rise to concerns regarding the reliability of patient reports and the risk of generating false signals.[31] The misattribution of adverse symptoms by patients to a newly started medication (i.e. the nocebo effect) can be influenced by many factors. This effect is more likely to occur in patients who expect to experience side effects, including patients who have previously experienced ADRs, and patients with certain psychological

characteristics, including anxiety and depression.[32] Misattribution is even higher when patients are specifically asked about drug side effects and can be stimulated by media reports of drug effects or class-action lawsuits.[32] These factors also give rise to the risk of malicious or false reporting by patients.[33] For all of these reasons, patient reports can be expected to generate a lot of "noise," which may make legitimate signal detection challenging.

However, various systematic literature reviews and international surveys have found patient reports to add value to pharmacovigilance by generating new potential signals.[23 34 35] These studies demonstrated that although the added "noise" from patient reports caused some potential signals to be lost, the actual combination of patient and HCP reports was useful for detecting new, legitimate signals. Consequently, the added scientific value of patient reports has been widely recognized by regulatory bodies in major markets around the developed world that have patient reporting systems in place.[34 35] However, the impact of further increasing the volume of patient reports on signal generation and the true value of patient reports in comparison to HCP reports on pharmacovigilance will need to be evaluated based on further comparative evaluations.[36] Consequently, further validation is required to demonstrate the reliability of data from initiatives targeted at increasing lay-sourced reports within proposals to enhance ADR reporting systems. However, the potential benefits of leveraging this possible data source do merit further analysis.

2b) Using the Internet for Collecting ADR Reports

A possible new source of drug safety information from laypersons is a myriad of interactive web pages used by the public for sharing personal experiences, such as social networking sites, blogs, discussion forums, etc. In Canada, this is a relevant source of information since over 80% of Canadians were internet users as of 2009[37] and almost 70% of these individuals were using the internet to search for medical or health-related information.[38]

The internet now makes it possible to collect the highly sought-after "real-world" data in the truest possible sense, under the kinds of conditions than could

never be planned for in a phase IV study. Many online disease-related communities share individual experiences with illness, and are therefore likely to mention treatment outcomes, including drug side effects or treatment failure. Consequently, social media sites can contain ADR reports that may be useful for safety data mining activities, potentially allowing signals to be generated, detected and assessed much more quickly than via traditional adverse event (AE) data collection methodology.[39]

While the internet is a potential new source of ADR reports, this is a new approach with no regulatory guidance or industry standard best practices on how this data source should be handled.[40] Consequently, there is a need to evaluate how using ADR reports from social media can contribute to drug safety surveillance efforts in a meaningful way. Additionally, regulators will need to define how information from these sites should be handled with respect to reporting collected individual case reports to health authorities. Given the sheer volume of available online data (for example, a single social networking site has been shown to contain over 3000 potential AE reports[41]), drug companies and regulators lack the resources to process these reports in the same way that other cases from spontaneous reporting systems are currently handled.[39]

The underlying challenge to be addressed is that current ADR-related regulations were developed to support a data collection system based upon scarce information, thus the current regulatory reporting rules no longer apply.[40] For example, in Canada, drug companies are required to routinely screen relevant local literature publications for any mention of ADRs involving their products.[42] While pharmacovigilance legislation does not currently mandate screening the internet for ADR reports, regulations do require drug companies to document, assess, and potentially report to health agencies any AEs for their drugs that they become aware of, from any report source, including the internet.[42] Consequently, if drug companies were to proactively seek out ADRs on social media sites, they would be faced with an unmanageable workload, requiring extensive pharmacovigilance resources, and would also increase the workload for the health agencies that would subsequently receive these reports. Due to these

implications, routine screening of social media sites for ADRs is not currently being performed (with exceptions for industry-sponsored websites) and drug companies are more inclined to avoid websites that may provide valuable insights on patient habits and community health needs.[40]

In the absence of regulatory direction regarding how these particular ADR reports should be collected and handled by industry, there is a disincentive for industry to seek out this potentially worthwhile information. Since current legislation is founded upon concepts that were developed when abundant safety information was not readily available the way it is today, this wealth of safety and efficacy data does not fit into the current Canadian framework for pharmacovigilance. In order to identify a scalable, operational solution for internet-sourced ADR reports, regulators will need to address the current pharmacovigilance system as whole, noting that by increasing the number of AE reports handled by drug companies, there may be a need to increase the capacity of regulators to subsequently deal with these reports.[40] For example, this may be achieved by handling internet-sourced reports in an aggregate manner for signal assessment purposes, without having to comply with the current requirements for individual case reporting.

Due to the novelty of the concept of using the internet for ADR reports, there is a lack of public data demonstrating how safety information collected online can be used to detect new safety signals. However, there are at least two different methods for collecting ADR data that merit further consideration: using automated methods for scanning the internet for ADR reports, and using internet-based intensive monitoring systems.

A pilot study has provided preliminary evidence on the validity of data from health-related social networks, with the frequency of reported ADRs generally found to correlate to the documented incidence of ADRs in product labels.[41] This study used a programmed web crawler to automatically screen and collect user comments from a health-related site used by patients to join disease-related support groups. Relevant user information (drug treatment name, disease name, and comments) were extracted from user posts and comments were

screened for AEs. Although this required translating lay expressions into coded standard medical terminology, this procedure already exists in spontaneous reporting systems, so it did not represent an additional data processing step. Lastly, the frequency of reported AEs was compared to the documented incidence of adverse reactions for specific drugs, which were found to correlate.[41]

However, this new approach raises a variety of concerns regarding the reliability of internet-sourced reports. For example, these systems can be prone to reporting biases in that patients are more likely to comment on adverse symptoms that they experience in more direct ways, such as fatigue or weight gain, rather than conditions detected via formal testing, such as elevated cholesterol.[41] Additional concerns include the rate of false positives, the possibility of duplicates, and the inability to substantiate individual ADR reports, given the often limited quantity and quality of reported information. Furthermore, due to the lack of possible follow-up with patients to collect further case details, the ability to conduct a meaningful medical assessment of an ADR from social media sources is limited.

In order to address some of these concerns, the development of online drug safety monitoring methodology can be modeled from signal detection techniques already being used for other important areas of public health, such as epidemic intelligence. Internet-based surveillance technologies are being increasingly used for the identification of disease outbreaks and can serve as a model for developing web-based systems for the detection of drug-related safety signals.

These "syndromic surveillance" techniques have been shown to effectively detect signals of emerging infectious diseases by screening publicly available online information on health-seeking behavior, in the form of search terms entered into engine queries and news media reports.[43–47] In general, these monitoring programs use automated systems to collect data from a multitude of sites (e.g., as many as 20,000 different sources every hour[45]), which are then analyzed, interpreted and disseminated to various public health officials for further investigation or regulatory action, as needed. Internet search volume

activity has even been found to correlate to the seasonal and geographic occurrence of certain medical conditions (e.g. kidney stones), and consistency with insurance claims data has validated internet search volume activity as a potential surrogate for disease incidence.[48]

The use of search detection algorithms for internet-based disease monitoring is still being explored with respect to the sensitivity and specificity of data analysis. Nonetheless, these techniques have already shown valuable potential benefits, including reduced operational costs, increased reporting transparency, and earlier signal detection in comparison to traditional epidemic surveillance systems.[46–48] Since syndromic surveillance programs can help to identify disease outbreaks faster than conventional epidemiology, they can inform health officials and the public earlier, in order to enable them to take necessary precautions against infection.

Similarly, online drug safety monitoring programs offer the potential to detect drug risks earlier than traditional ADR reporting programs, enabling more timely regulatory action, as needed, and more informed treatment choices. Internet surveillance thus represents an important advancement in public health monitoring and merits further consideration for application in the field of pharmacovigilance. Validated data collection and analysis methodologies are needed to demonstrate the value of internet-sourced reporting, which should be based on input from all relevant stakeholders (regulators, patients, HCPs, industry, etc.).[33]

Another noteworthy online ADR reporting mechanism is the use of internet-based intensive monitoring systems designed specifically to solicit ADR information from patients, which may be particularly useful in prescription event monitoring programs. Traditionally, prescription event monitoring is a system whereby patients issued prescriptions are tracked using healthcare databases or questionnaires sent to prescribers at regular intervals.[49] However, given the large use of healthcare resources needed to manage these programs, prescription event monitoring would be less costly if it involved patients (instead of HCPs) as the information source. This can be achieved by issuing online ADR questionnaires

to patients who are dispensed medications over a specified period of time and can be especially useful for eliciting ADR reports for newly approved drugs. Automated web-based reporting systems thus enable rapid and ongoing surveillance that can provide results to drug companies and health authorities in near real-time.[50] Consequently, web-based intensive monitoring can be used to gather data about the time course of ADRs, which isn't possible using traditional reporting methodologies.[51] This is significant since longitudinal drug safety knowledge can have important implications for adherence, as patients may be motivated to stay on medication if they know to expect when an ADR may occur, how long it will persist and whether it will go away on its own.[51] Since internet-based reporting systems facilitate the reporting of ADRs by patients, they can potentially increase passive reporting rates and thereby enhance drug safety surveillance in a short period of time, potentially providing an early warning for ADRs at the population level. Internet-based reporting systems have already been found to be effective for the active monitoring of AEs experienced following vaccine administration post-licensure in various mass immunization programs.[50] [52–54] However, further research is needed to verify the validity of internet self-reports for other drugs prescribed as part of routine clinical practice.

A limitation of this approach is interference by the nocebo effect, since patients enrolling in an ADR monitoring program will likely be more sensitized to the possibility of experiencing drug side effects and may be prone to causal misattribution. Furthermore, since patients enrolling in these programs are more likely to have been informed of possible drug side effects, either from their HCP or from the drug label, they may be more attentive to ADRs that are already known for the drug. Consequently, further validation is needed to clarify the ability of this approach to identify unexpected or less common ADRs.

Another limitation of internet-based ADR collection technologies is the concern that the results of these systems may under- represent groups with limited access to the internet, such as patients who are hospitalized, illiterate, or who can't afford a computer. This may also be an issue for elderly patients in Canada since approximately 41% of them are internet users compared to almost 97% of

individuals under 34 years old.[37] However, further research is needed to clarify whether family members or care givers of these patients compensate for their lack of online activity by reporting on their behalf.

Another issue in relation to using ADR reports from online social media is whether the collection of personal information posted on the internet is ethical, given the sensitivity of patient information. Internet users generally share information within the context of defined social communities that would typically be accessed primarily by other users with the same vested health interests. These users may be less inclined to post personal details if they were aware that a web-crawler was actively seeking and documenting their private experiences, and forwarding their information to pharmacovigilance officers and regulators around the world. Some individuals may even be appalled by the thought that the very same company whose medicine caused them to have a serious side effect was actively collecting, analyzing, sharing and indefinitely storing their personal information. This concern may be greater for more vulnerable populations, such as younger generations, who may be more likely to use social networking sites and more willing to openly share personal facts online without considering the possibility of undeclared "data mining" of their information.

While regulators do have an obligation to enforce the protection of individuals' private information, the privacy policies of social networking sites generally specify that posted comments are publicly available to all users. Consequently, the collection of this information for safety monitoring purposes does not pose a privacy violation from a legal perspective, as long as the data collection respects the website's terms and conditions for use.[41] In addition, Canadian legislation allows an organization to collect personal information without the knowledge or consent of the individual if the information is already publicly available.[10] Moreover, this type of risk is not exclusive to ADR data collection as it is generally applicable to any kind of information posted online. Patient privacy concerns are related to the larger issue of internet security and the protection of personal information, a responsibility which resides primarily with the actual user posting information (or in the case of minors, with their parents or

legal guardians). Furthermore, the previously mentioned safeguards in place at drug companies help to protect data privacy and can be applied to data handled in an aggregate manner, which would be the ideal method for processing unstructured internet activity data.

Another possible concern about the use of web-based monitoring programs is the potential cost of implementing these systems. However, the costs of web-based data collection systems are actually substantially lower than those of traditional AE surveillance methods, as shown in a recent H1N1 vaccine internet prescription event monitoring system for patients, whose design, maintenance and administration only required a total of about 50 working hours, making it an affordable method for collecting ADR reports.[41] Furthermore, the shift to active drug safety monitoring should be seen as a long-term healthcare investment strategy, given the high costs of prescription drugs and the burdens of ADRs on the healthcare system. It is more cost-effective to evaluate expensive medications properly, in order to learn of their risks sooner, rather than to use public funds to pay for drugs that cause dangerous side effects that will further strain public healthcare resources.[55]

3. Post-Approval Drug Trials

3a) Incentives for Company-Sponsored Research

As part of Health Canada's shift towards active pharmacovigilance, the lack of well-designed post-approval drug studies should be addressed so that safety and effectiveness continue to be investigated post-licensure. This is important for ensuring that regulators are able to protect public health by having strong science on which to base their decisions.[56] This is also important for ensuring that valuable healthcare resources, including the time invested by clinicians in post-market research, are allocated to worthy activities.

In the upcoming progressive licensing framework, Health Canada would ideally have the authority to mandate specific requirements to drug companies, such as post-market safety studies, for drugs whose risks may potentially

outweigh the benefits. Under current legislation, Health Canada has the authority to request from a drug company any relevant information or material regarding a new drug that it considers to be necessary for assessing safety and effectiveness.[57] Although this allows Health Canada to request the collection of additional trial safety and effectiveness data from manufacturers, it does not allow Health Canada to withhold or withdraw a drug's approval based on the resultant data collection. Ideally, enhanced legislative authority as part its new lifecycle approach would enable Health Canada to grant a conditional approval to drugs that would otherwise qualify for a RMP, in order to ensure ongoing characterization of drug benefits and risks, without delaying access to new therapies. More specifically, Health Canada would determine whether specific post-marketing interventions (e.g. patient registries, post-marketing study) are needed for reducing specific risks to patients, and these interventions would be the conditions of approval. This could include requirements to specify important features of mandated post-marketing commitments, such as study objectives, protocol design, key end points, safety monitoring schemes, etc.[56]

This proposal represents a dramatic change to Health Canada's current conditional approval process, which was designed specifically in response to the need for access to new drugs for serious or life-threatening conditions with no alternative treatments.[58] Health Canada grants conditional drug approval to pharmaceutical companies on the basis that specific requirements will be fulfilled post authorization. This currently may include drugs with surrogate markers predictive of clinical evidence but without evidence of efficacy based on clinical endpoints.[58] Commitments may include performing additional studies to verify clinical benefit, undertaking increased safety monitoring and reporting of certain events, providing educational materials, and abiding by restrictions on drug advertising and labelling.[56] The current conditional approval guidelines involve undertaking a trial to confirm improved clinical outcomes based on surrogate markers, whereas this scope would be broadened to include drugs that would otherwise qualify for an RMP (i.e., where evidence is needed to confirm that the benefits of a drug outweigh the risks).[57 59]

In contrast to the RMP system being developed by Health Canada, this proposal can be more practical for stakeholders, including industry, for multiple reasons. Firstly, this approach would provide greater transparency, since post-marketing commitments in relation to conditional approvals are accessible on Health Canada's website, unlike RMPs, which are not publicly available in Canada.[60] Secondly, although many changes to the existing framework would be needed, the core process for issuing and complying with conditional approvals has been in place for almost 25 years,[56] which would mean spending fewer public funds on organizational changes than creating a completely new review program. Thirdly, Health Canada would be able to closely monitor the safety and effectiveness of these drugs post-approval, through enhanced post-market surveillance initiatives mandated to industry. Post-approval studies that don't currently require regulatory review would be subject to review under the revised policy, to ensure that they are designed to address specific research objectives, in accordance with established scientific standards. Lastly, although this would delay the complete approval of new drugs, this would not be unfavorable for manufacturers as their drugs would still gain earlier market access with the conditional approval. Furthermore, having Health Canada's expectations made explicit would be more practical for drug sponsors than having to invest their resources in devising RMPs that may create unnecessary burdens for stakeholders and may result in negotiations that could delay market access.

Another method of promoting this type of research is through incentives to perform comparative effectiveness research. Post-market research would be more valuable if it involved more pragmatic clinical trials, that is, studies designed to answer questions faced in the real-world by patients, prescribers, funding agencies, and other decision-makers.[61] Comparative effectiveness research is becoming increasingly important for evaluating the clinical effectiveness and cost effectiveness of different treatment options for the same indication. The prevalence of me-too drugs makes it even more important to collect evidence on comparative risk-benefit profiles of medications, so as to support drug coverage decisions and associated treatment policies regarding first line therapies.

Consequently, these trials can be important for providing evidence-based knowledge that will guide prescribing practices by addressing important information gaps for pharmaceutical products.

However, many practice-oriented research questions, including those that require the use of head-to-head drug trials, can be very costly due to the large population of study participants targeted in post-approval research. Additionally, conducting these studies may pose conflicts of interest for drug companies, as the studies can be risky, from a commercial perspective, if they do not favour the sponsor's product. Consequently, once a medication has been approved, drug companies generally have few incentives beyond marketing to perform post-licensure drug research, and many important treatment-related questions remain unstudied. Due to the reluctance to proactively conduct comparative drug trials, regulators, prescribers, patients, and insurers must rely on indirect comparisons between placebo-controlled trials, which may be difficult for drawing conclusions, given the differences in study design. Moreover, significant discrepancies between direct and indirect comparisons of competing interventions suggest a need for caution in relying on indirect comparisons for drawing firm conclusions.[62]

Consequently, there is a need for increased head-to-head post-marketing studies in order to collect comparative safety and effectiveness data. A possible option encouraging these studies may be to create incentives through Health Canada's Office of Patented Medicines. This type of approach is currently in place for promoting pediatric drug trials. Health Canada currently offers a six month extension on a drug's data protection in exchange for a clinical trial designed to increase knowledge about the use of a drug in pediatric patients, when conducted within five years of drug approval. The objective of this policy is to learn about the effects of drugs in pediatric populations in order to develop more informative product labels, even if the intent is not necessarily to expand the indication to include pediatric patients.[63]

This concept can be adapted to increase the willingness of drug companies to design and conduct comparative drug trials. This would ideally involve a

requirement for sponsors to plan their trials in consultation with Health Canada, in order to ensure regulatory oversight with respect to study objectives and trial design. This could also help to minimize study duplication in order to promote efficient use of clinician-investigators, and should include a requirement for sponsors to accurately publish the study results.

This approach may be enticing for pharmaceutical companies as it can help to safeguard their brand's market exclusivity from the threat of generic drug manufacturers. However, this may be more worthwhile for blockbuster drugs with revenues that exceed the costs of conducting large-scale post-approval drug studies. Industry consultation may be needed for determining the length of the data exclusivity extension that would make this incentive successful. By defining this new policy as clearly as the current pediatric rule, drug companies will have the option to pursue comparative effectiveness studies in exchange for extended data protection on their drug submissions in order to delay the entry of generics, creating a mutually beneficial situation.

3b) Enhancing Independent Post-Approval Research

Although formal incentives for industry will help to promote the conduct of well-designed post-approval research, they will not necessarily ensure that key research questions are being addressed, since industry-sponsored research will likely continue to be driven by commercial interests.[64] Consequently, there is a need for the conduct and analysis of post-approval drug safety and effectiveness studies by arm's length research centers.

In an attempt to increase independent post-approval research efforts, Health Canada and the Canadian Institutes of Health Research have established a government-funded research association entitled the Drug Safety and Effectiveness Network (DSEN). The DSEN consists of Canadian academic research centers conducting post-market drug studies in a broad range of areas, including pharmacogenomics, safety surveillance, and comparative effectiveness. The objectives of this association are to provide useful evidence to regulators,

policymakers, patients and HCPs, and to increase Canada's capacity to conduct high-quality post-approval research.[65] The DSEN evaluates funding applications according to scientific merit and potential impact on health outcomes, practice, programs and/or policy.[66] The independent nature of this program allows for impartial trial objectives and study design, which may give increased credibility for drugs whose study results are favourable.[64]

While the intent of the DSEN is laudable, the usefulness and sustainability of this network remain questionable, given the use of limited public funds and the vast potential research areas worthy of support. The DSEN was introduced in 2007 with investments of $32 million over 5 years and $10 million per year thereafter from public funding.[65] However, given the wide range of potential research questions to be addressed and the ongoing approval of new drugs, the DSEN has acknowledged challenges in reviewing, prioritizing and funding numerous project proposals competing for limited resources.[67] Inadequate funding to support research networks thus threatens the sustainability of independent health research in Canada and the feasibility to plan studies in emergent priority.[64]

A new sustainable source of funding for third party health research is therefore needed. Given the high profit margins of drug companies, in contrast to the limited supply of public healthcare dollars, a logical source of funding for third party research is the pharmaceutical industry. Italy may serve as a model for such funding, where drug manufacturers are required to contribute approximately 5% of their promotional budget to the Italian regulatory authorities to fund independent post-market research.[68 69] The scope of promotional costs in this calculation excludes salaries of marketing and sales staff but includes expenditures for promotional activities that target HCPs in Italy, including advertising, visual supporting materials, seminars, etc., resulting in an approximate contribution of 45 million Euro per year.[68] This is part of Italy's regulatory approach to promote independent drug research in order to collect useful, reliable data.[70] Although there is little evidence of whether industry-sourced funding in Italy has specifically enhanced phase IV research, in Canada,

this funding model could be specifically designed to support independent post-approval research bodies, such as the DSEN. This can be applied as a type of "mandatory philanthropy" for the pharmaceutical industry, in exchange for the same tax deductible incentives currently in place for corporate charitable donations.

Another concern about the DSEN is that there is still no indication of whether it is able to support research reflective of patient needs, rather than those of insurers or policy-makers. While clinicians may look to pragmatic trials to ensure that their patients receive the best care, drug plan and formulary decision makers are interested in the results to ensure that their resources are used as efficiently as possible. These latter groups allocate their limited budgets to interventions that offer the highest return on investment or health benefit, resulting in decisions that may restrict access to certain drugs for patients.[71] Consequently, if post-approval trial findings are used to generate broad decisions based on risk-benefit ratios for a population at large, without consideration to specific sub-populations that may not benefit in the same way, this may limit options for patients whose care requires treatment outside of large-scale results.

In the context of limited resources, research priorities need to be set and rigorous and transparent methodology must be used, including evaluation of applicable treatment options and systems, and thorough processes for evaluating benefits in special sub-populations. Whenever possible, large-scale funding and treatment decisions based on these trials should recognize individual patient preferences (e.g., drug administration, tolerance for adverse reactions, etc.) and differences in response to treatments so that patient choices are not limited by drug coverage decisions. Accordingly, the DSEN application review process should ideally involve input from patients or patient representatives, which may include their physicians, to ensure that patient perspectives and interests are considered in advance. Although the current DSEN funding application review committees do involve community reviewers, their role is limited to commenting on the clarity of the language used to explain proposed research to the public and for presenting a selection of lay abstracts to the committee.[66]

The DSEN may be able to learn in this regard from an independent non-profit organization created in the US by Congress in 2010, entitled the Patient-Centered Outcomes Research Institute (PCORI).[72] Like the DSEN, the main objective of PCORI is to promote the conduct of high integrity, evidence-based research on medications. However, unlike the DSEN, PCORI's research specifically focuses on comparisons and outcomes that matter to patients, including individual preferences, autonomy, needs, and impact on function, symptoms, and health-related quality of life. To this end, PCORI's research initiatives are guided by patients, caregivers and the broader health care community, and include a wide range of settings and participants to address individual differences and barriers.[72] This is achieved by integrating patient and stakeholder input through a variety of activities, including public consultations, opportunities to review research applications, engagement workshops, and opportunities to provide feedback directly on its website.[73]

The DSEN review committee should similarly incorporate input from patients and care givers in order to ensure that the patient viewpoint is well represented during the review process. This will be helpful for assessing the perceived worth of clinical questions, for identifying ideal comparators in specific therapeutic areas,[74] and for pre-defining measures for the interpretation and use of results, including potential impact on subsequent large-scale treatment and funding decisions.

Conclusion

This chapter has presented multiple proposals for addressing the current knowledge gaps in pharmacovigilance and has drawn upon existing, practical policies and models to support the feasibility of these options. These include methods that facilitate reporting by HCPs through the use of electronic health records, in addition to alternative report sources, such as internet-based reports from patients. In order to adopt these online information collection options, drug companies will look to Health Canada for clear guidance on the reporting requirements for unstructured online ADR data so that they can become proactive

in seeking out this potentially rich, new data source. Although further evaluation of electronic reporting mechanisms is needed to continue to validate and optimize them as ADR reporting systems, the successful application of web-based technology in other health-related contexts warrants further investigation of this methodology in pharmacovigilance.

Another proposal is to broaden the scope of Health Canada's existing conditional drug approval policy in order to mandate specific post-marketing commitments to drug sponsors in lieu of having them propose their own RMPs. A further option is to create formal incentives for industry to conduct comparative effectiveness studies using data protection extensions. Both of these approaches would enable Health Canada to have direct oversight of phase IV studies, in order to ensure that they are being adequately conducted and that healthcare resources are being justly applied to causes that will best serve the public. Finally, by implementing a sustainable funding model for objective third-party research and ensuring that the DSEN contains adequate patient representation, Health Canada would be able to promote the production of knowledge to fill the current gap in pharmacovigilance, in order to help guide informed treatment decisions.

Health Canada is currently contemplating the development of formal RMP policy that will impose more requirements for drug companies and HCPs.[75] Since the proposals in this chapter are mutually beneficial to stakeholders, they may be practical alternatives to RMPs. However, selection of any of these solutions will require the reallocation of resources at the regulatory level and legislative changes to execute these proposals. There are thus various factors to be considered in determining which of these options will be the most effective and the most efficient to implement, in order to determine the most value-added methods for improving drug safety surveillance. The following, concluding chapter will make recommendations for the next steps needed to update Health Canada's current pharmacovigilance system.

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Chapter 5 – Conclusion: Next Steps Towards Proactive Surveillance

Adverse drug reactions (ADRs) can be dangerous and are a heavy strain on the health care system. Information on drug risks is important for enabling health care professionals (HCPs) to make informed treatment choices with individual patients and to monitor them accordingly. Patients, HCPs, and health care systems thus rely upon the timely collection of new information on drug safety and effectiveness.

Since the safety profile of medications evolves as new information emerges in the post-market setting, there is a need for regulators and drug manufacturers to continuously reassess the risk-benefit profile of approved medications in the context of this new evidence. The delayed identification of a new safety signal means that HCPs and their patients are not informed as quickly as they should be of information that may impact treatment decisions and patient well-being.

This thesis has identified the main limitations of spontaneous adverse event reporting systems and post-marketing studies, two of the key activities used for collecting post-approval drug safety and effectiveness data. Spontaneous adverse event reporting systems are primarily limited by under-reporting of ADRs by healthcare professionals, due to time constraints in submitting these reports. Consequently, in order to generate increased ADR data, there is a need to facilitate spontaneous reporting mechanisms and/or ADR data collection systems. Post-approval studies suffer from variable implementation due to a lack of incentive for industry to perform these studies, and poor study design due to conflicts of interest for industry. As a result, these studies have gained a poor reputation, which has led to distrust in evidence arising from them. There is thus a need to ensure that adequately designed post-approval drug studies are being performed to legitimately contribute to scientific information. Consequently, while spontaneous adverse event reporting systems and phase IV clinical studies may provide important information about marketed drugs to help inform patients

and prescribers, additional proactive measures are needed to address their limitations, so that reliable information can be obtained more quickly.

The risk management program (RMP) policy being developed by Health Canada may help to mitigate some of the risks associated with medication use. However, RMPs are of limited value as they do not eliminate the need for improved systematic surveillance. RMPs are generally not intended to detect new safety concerns and thus do not address the need for proactive drug safety and effectiveness monitoring. Additionally, RMPs lack standardization across industry, resulting in different safety standards for similar drugs and/or risks. Furthermore, RMPs can be burdensome for HCPs and may therefore not be widely implemented at the patient level. This can be especially problematic if risk management strategies are seen by regulators as sufficient for offsetting the risks of a drug that would otherwise not be approved, potentially resulting in reduced standards for safety and efficacy.

A lifecycle approach to drug regulation may help to ensure that approved medicines are re-assessed on an ongoing basis. Health Canada is prepared to pursue new legislation to support the legal framework for this initiative, as needed, in order to implement more effective and efficient surveillance practices, and is interested in adopting new value-added, proactive measures for pharmacovigilance.[1]

In alignment with Health Canada's modernization interests, a variety of proposals have been made for addressing the current gaps in pharmacovigilance. These include facilitating ADR reporting by HCPs through the use of electronic health records, in addition to seeking out alternative report sources, such as patient ADR reports, using automated methods for scanning the internet or internet-based intensive monitoring systems. Proposals for enhancing regulatory oversight of post-marketing studies include broadening the scope of Health Canada's conditional drug approval policy, in order to mandate specific study commitments to drug sponsors, and creating formal incentives for industry to conduct comparative effectiveness research using data protection extensions. These approaches would help to ensure that phase IV studies are being adequately

conducted and that healthcare resources are being justly applied to causes that will best serve the public. A possible method for supporting ongoing, objective, third-party research, such the Drug Safety and Effectiveness Network (DSEN), is to implement mandatory funding from the pharmaceutical industry as a sustainable new funding model. A further recommendation for helping to ensure that the DSEN's research has a patient-centered focus is to increase patient representation on DSEN review committees, whenever possible.

There are at least four important factors that are needed in order to evaluate whether modernization initiatives will successfully improve patient safety. Firstly, regulatory foresight is needed to anticipate how the interplay between scientific developments, demographic trends, and evolving societal attitudes may lead to new challenges related to drug regulation.[2] Regulatory experts need to ensure that they stay abreast of advancements in science and technology and to consider epidemiology patterns that may lead to shifting population health needs. This is important for ensuring that Health Canada's new framework addresses both the short term and longer term issues that may arise in relation to new drug submissions, in addition to issues related to the ongoing surveillance of existing therapies. Tools used in Health Canada's new framework should be prepared to address the new kinds of challenges that may arise. These may be determined by surveying the patent literature,[2] and through its existing collaborative relationships with regulatory counterparts in other major markets, such as the EU, the UK, the US, and Australia, which will also promote alignment.

Secondly, ongoing feedback from relevant stakeholders will be needed regarding the selection of new vigilance activities. This is important for assessing feasibility with respect to the impact of regulatory policies at a practical level, and for ensuring the application of sound scientific principles in the implementation of innovative methodologies, such as the use of electronic ADR reporting technologies. This may need to involve piloting various approaches with academic researchers or drug companies in order to validate new methodologies.

The reaction of pharmaceutical companies to new regulatory requirements may be unfavourable in the short-term, given that additional regulatory responsibilities, including the conduct of mandated post-approval studies, can be costly. However, drug companies are aware that inadequate responses to safety issues can have serious consequences for patient health and can threaten drug makers both financially and at the reputational level. Consequently, pharmaceutical companies do have long-term interests in ensuring that the risk-benefit profiles of their medications are continuously monitored.[3] Furthermore, drug companies are more likely to support new surveillance requirements if they are included as part of Health Canada's consultation process.

Thirdly, the development of adequate regulatory guidance will be needed regarding how new activities should be carried out, in order to provide clear standards for industry, to ensure consistency in their implementation. For example, Health Canada's current guidance documents will need to be amended to describe how safety data from new sources should be collected and evaluated for submission by drug companies, and how it will then be used at the regulatory level. This is another area that can benefit from stakeholder consultation, in order to promote clarity and practicality.

Lastly, regulators should find ways to measure the effectiveness of new pharmacovigilance measures in carrying out their objectives, an evaluation which Health Canada has acknowledged to be important.[4] This is important for ensuring that implemented changes can be monitored for their impact on relevant stakeholders.

Regulatory modernization initiatives should focus on ongoing drug evaluation methods that support sound regulatory decision-making and reflect the ethical commitment to protect patient safety.[5] In order to maximize its ability to protect public health, Health Canada should be utilizing the best means of collecting information to ensure that a drug's benefits outweigh the risks. In the current context of limited health care resources, investing in new, more efficient methodologies for collecting drug safety and effectiveness data warrants consideration. By strengthening post-marketing surveillance systems, regulators

will be taking a proactive stance in the governance of medications throughout their lifecycle and HCPs will be able to more assuredly choose the right treatment options with their patients.

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