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Health Product Vigilance Framework

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Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.

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1 Introduction

1.1 Purpose Statement

The Health Product Vigilance Framework is intended to serve as an evergreen document that captures Canada's current product vigilance system and conceptually describes Canada's future integrated product vigilance system that will be developed over the next three to five years.

1.2 Vision

Health Canada's vision is to continually promote high standards of product vigilance for the protection of the health and safety of Canadians, and to facilitate access to products vital to the health and well-being of our citizens through a "lifecycle approach" to product vigilance. Health Canada will be an international force in the field of product vigilance, which will lead to increased public confidence in the products Canadians rely on for their health.

1.3 Public Confidence

Because of the increasing number and complexity of products used by Canadians to maintain and improve their health, it is important that Health Canada's product vigilance system remain open, transparent, accessible and accountable. Products available for sale in Canada have undergone a rigorous assessment and meet high standards of safety, quality and efficacy. The continued safe and effective use of these products depends on a thorough and ongoing understanding of the benefit-risk as they become known through real-world experience.

1.4 The Need for a Canadian Health Product Vigilance Framework

Two federal initiatives, the Blueprint for Renewalⁱ and the Food and Consumer Safety Action Planⁱⁱ, have aimed to modernize Canada's regulatory system for therapeutic and consumer products so that it can respond successfully to changes in the regulatory environment and better protect the health and safety of Canadians. This shift will be achieved through the implementation of a lifecycle approach to regulating health products, an approach already used by other leading regulators. The Food and Consumer Safety Action Plan aims to improve Canada's existing processes by anticipating and preventing problems before they arise, targeting products that present the highest risks, and providing rapid response to problems when they occur.

The Health Product Vigilance Framework is being developed to strengthen and modernize health product vigilance (PV) practices in Canada. Aligned with the Federal Regulatory Post-Market Surveillance Strategyⁱⁱⁱ, this framework will optimize resources by focusing on higher risk products through standardized prioritization policies and will implement a vigilance framework that manages risks consistently across product lines. It will emphasize industry's vigilance responsibilities, consistent with international harmonization objectives, wherever possible, and will integrate the use of product vigilance tools across product lines and throughout a product's lifecycle.

The rationale behind the development of this framework is to:

- have a coherent, integrated approach to product vigilance within the Health Portfolio and across product lines;
- strengthen regulatory processes around product vigilance;
- provide clarity and transparency around how Health Canada performs product vigilance and what industry's role is regarding product vigilance; and

- align product vigilance with international best practices, where possible.

The framework will be an overarching model for how Health Canada views health product vigilance, will define the regulatory philosophy and policy direction, and will outline the structure and priorities to guide the development of the product vigilance tools over the next three to five years. It will provide a common basis for health product vigilance across product lines and will guide Branch staff, sponsors and other stakeholders in the use of the vigilance tools.

1.5 Scope of Framework

This product vigilance framework considers all Health Products and Food Branch (HPFB) regulated health product lines and associated vigilance activities, including data collection, monitoring, processing, evaluation, risk communications and market interventions that will support and enhance surveillance throughout a product's lifecycle.

A step-wise approach to implementation of new vigilance tools will focus on the evaluation of clinical outcomes and will begin with higher risk pharmaceutical and biologic products.

Vigilance activities are concerned primarily with the safety and effectiveness of products in clinical use rather than their quality issues. Although the Lot Release Program and the Yearly Biologics Product Report (YBPR) are essential activities for ongoing monitoring of the quality of biologics, with potential implications on product safety, they are outside of the scope of this document. Good Manufacturing Practices, which are concerned with product quality, are also outside the scope.

1.6 Structure of the Framework

As the interrelation of product vigilance activities and tools becomes more complex, and as innovations in the field of product vigilance continue, there is a greater need for the development of a framework to guide the current and proposed product vigilance program. At play are innovations in vigilance tools and technologies that will support the development, integration and use of the tools. This framework will identify the vigilance tools and explain how they will operate within the Department. Health Canada will update this framework periodically as new vigilance tools are developed and integrated into the health product vigilance system.

1.7 Product Vigilance – International Context

Canada operates in an increasingly complex environment influenced by a number of factors, such as public expectation and awareness, evolving science and technology, the global regulatory environment and government priorities. These factors influence how Health Canada carries out its mandate and delivers programs and services to meet the evolving needs of Canadians. They may also reinforce the need for coordinated government action, partnership and collaboration. With the increased availability of product information, the field of product vigilance is evolving rapidly.

Global trends include a shift in emphasis from passive to more proactive vigilance methods, as well as increasing pressure for a fast and efficient health product approval system, wherein marketed health products are used as safely and effectively as possible.

Globalization is opening new avenues for international cooperation. Canada looks to and collaborates with regulatory counterparts such as the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA), the American Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) for information and partnership on product vigilance activities. There are similarities in central elements of these vigilance systems, including:

- a shift towards a proactive, lifecycle approach to regulating all health products;
- participation in and the adoption and implementation of the International Conference on Harmonisation (ICH) guidelines for health product vigilance;
- participation in the Global Harmonization Task Force (GHTF) for medical devices;
- attention to both clinical trials and real-world use; and,
- a desire to strengthen and align product vigilance legislation and guidelines with those of other regulatory authorities.

1.7.1 European Union

On December 31, 2010, the European Union (EU) published new pharmacovigilance legislation^{iv} to strengthen and rationalize the current Europe-wide system for monitoring medicinal products for human use. These strategies include: clarifying roles and responsibilities for industry and regulators; greater transparency; rationalizing oversight of the market authorization holders (MAHs) pharmacovigilance systems; clarifying the legal provision for risk management plans; simplifying periodic safety update reporting (PSUR) and single case adverse drug reaction (ADR) reporting and applying these requirements in a manner proportional to risks; and providing a strengthened legal basis for the request of post-authorization safety studies. In addition, through risk minimization activities, the MAH will be required to address the potential for medication errors and state how this risk has been addressed in the final design of the pharmaceutical form, product name, information and packaging.

1.7.2 United States

The United States (US) has strengthened drug safety legislation by signing into law the Food and Drug Administration Amendments Act (FDAAA)^v. This Act provides further powers to the FDA to require post-approval studies or clinical trials, the submission and implementation of a Risk Evaluation and Mitigation Strategy (REMS), pre-review of direct-to-consumer advertisements, and requests that safety information be included in labelling.

Under the re-authorization of the Prescription Drug User Fee Act (PDUFA IV)^{vi} signed into law on September 27, 2007, the FDA stated it would use user fees to implement various measures to reduce medication errors related to look-alike/sound-alike names, unclear label abbreviations, acronyms, dose designations, and error-prone label and package design. A dedicated unit has been established to review data from a real-world use safety perspective.

1.7.3 Australia

The Australian Therapeutic Goods Administration (TGA) has a guideline for pharmacovigilance responsibilities for sponsors of registered (authorized for market) medicines that includes adverse reaction reporting and reporting requirements in special situations. Recent legislative amendments^{vii} have enhanced both pharmacovigilance suspension provisions for medicines, and risk management plan requirements for selected prescription medicine products as part of pre-market applications. TGA has formally adopted the EU Guideline Volume 9A format (EU-RMP) for risk management plans. In addition, the TGA can mandate a sponsor to change an existing health product name/package/label when patient safety issues arise.

1.7.4 International Lessons Learned

As the field of product vigilance evolves, lessons can be learned from both recent legislative changes across jurisdictions and from international work which highlights the need to implement marketed programs on a risk-prioritization basis. First, consideration should be given to a product's overall benefit-risk characteristics when developing vigilance requirements. Second, consideration should be given to resourcing and review capabilities of the regulator, prior to legislating vigilance activities. Third, there is a trend towards focusing on risk management in special circumstances, such as in special populations, biosimilar products, and more advanced therapies. Fourth, a call for transparency with review activities is increasing. Finally, there is increased focus on the effectiveness of risk mitigation activities, of which risk communication is but one example.

2 Shared Responsibility for Product Vigilance

The maintenance and improvement of health and safety is understood to be a shared responsibility. In addition to government and regulated industry, health professionals, patients, consumers and their respective associations play an important role in reporting health product safety related issues. Health Canada is shifting its focus in the direction of encouraging and monitoring industry's good product vigilance practices, reflecting the fact that industry is responsible for the safety and efficacy of their products. At the same time, Canadians expect Health Canada to be involved in minimizing the risks associated with these products. As a result, there is a need for a robust yet transparent product vigilance system that will seek the appropriate level of involvement from the participants and stakeholders in the system.

Health Canada has committed to the full integration of ICH vigilance tools that will strengthen the current system and enable international work sharing and information sharing arrangements to proceed and continue into the future.

2.1 Market Authorization Holders

The MAHs have the primary responsibility for the safety of any products they sell, manufacture, import or distribute to the Canadian public and must comply with all Canadian legislative and regulatory requirements. The MAH must report promptly, to Health Canada, significant new information relating to the benefit-risk of their products^{viii}.

2.2 Health Canada

As a regulator, Health Canada is responsible for the regulatory regimes governing the safety of products including food, pharmaceuticals, medical devices, natural health products, consumer products, cosmetics, chemicals, radiation emitting devices, and pesticides. It also regulates tobacco products and other controlled substances and helps manage the health risks posed by environmental contaminants.

Health Canada is responsible for the regulatory oversight of the MAHs including the development, implementation and enforcement of legislative and regulatory controls, and maintains up-to-date safety information on health products which is communicated through a variety of means to health professionals, patients and consumers. The Department is committed to advancing public health through the authorization for sale of beneficial, innovative health products and by providing timely, evidence-based and authoritative information to allow consumers and health professionals to make informed decisions. Health Canada is responsible for taking appropriate action, when necessary, regarding the issuance, maintenance, amendment or revocation of market authorization. A further responsibility of the Department is to operate Canada's product vigilance system and to ensure that methods are in place to receive and manage vigilance data, monitor and evaluate that data, and manage the risks.

2.3 Health Professionals, Patients and Consumers

Although the regulation of medical professions does not fall under federal authority, practitioners play an important role in monitoring the real-world safety of health products by providing safety information to Health Canada and to product manufacturers on a voluntary basis. Consumers, patients and the general public also provide information on a voluntary basis. Health professionals, patients and consumers are encouraged to inform Health Canada of any problems they encounter (hazards, adverse reactions, malfunctions, and non-compliance) with regulated health products throughout their lifecycle including products used in a clinical trial setting. The physician also shares responsibility for the use of products prescribed to their patients. Practitioners, patients and consumers all play a role in deciding whether to use health products and it is important that they have access not

only to safe and effective products, but also to information that will increase the chances of successful treatment or prevention as the situation might require.

2.4 Partnerships, Alliances and Collaboration

For some health products, such as vaccines, blood, cells, tissues and organs for transplantation, where public health actions may be required as a result of safety concerns, it is also important for public health authorities to conduct safety surveillance. Public health surveillance includes the participation of the Public Health Agency of Canada, federal, provincial and territorial immunization programs, provincial and territorial blood programs and partners involved in transplantation.

The focus of public health surveillance is inevitably different than that of the regulator, given their different mandate and accountability. Public health surveillance therefore complements, rather than replaces, regulatory pharmacovigilance. Structures are in place to allow information sharing between Health Canada and public health partners as continued collaboration is mutually beneficial.

Partnerships, alliances and collaboration are key to improving and evolving Canada's product vigilance system. The following partnerships have been established to improve access to expertise and information:

2.4.1 The Institute for Safe Medication Practices Canada (ISMP Canada)

The Institute for Safe Medication Practices (ISMP) Canada is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives. The Marketed Health Products Directorate (MHPD) has worked with ISMP Canada since 2003 on the development and implementation of the Canadian Medication Incident Reporting and Prevention System (CMIRPS). Through this program, HPFB has access to information (in the form of medication incident reports) and expertise in the area of medication incident analysis and risk strategy development as it relates to Health Canada's role in improving safety and reducing the risk of medication incidents, particularly those involving health product names, packaging and labels. The clinical experience of ISMP Canada's staff, combined with expertise in medication incident analysis and risk strategy development, places the organisation in a unique position to offer a clinicians, patients or consumers perspective on safe and effective health products, particularly as it relates to health product names, labels and packages and their safe and effective use under real world conditions.

2.4.2 The Canadian Medication Incident Reporting and Prevention Program (CMIRPS)

The Canadian Medication Incident Reporting and Prevention Program (CMIRPS) is a collaborative program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of the program is to reduce and prevent harmful medication incidents in Canada. Health Canada contributes knowledge and expertise to CMIRPS in the area of medication safety from its perspective as the federal regulator of health products.

2.4.3 The Canadian Paediatric Surveillance Program (CPSP)

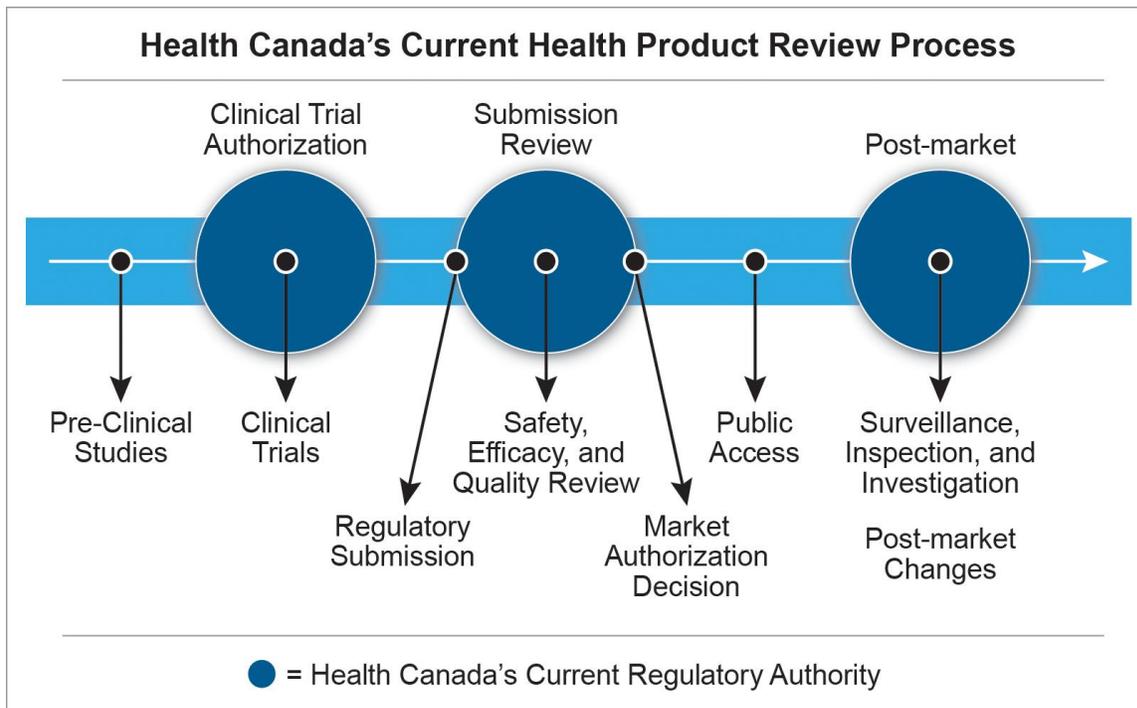
MHPD collaborates with the Canadian Paediatric Surveillance Program (CPSP) to encourage and support the reporting of serious and life-threatening adverse reactions in paediatric patients. The CPSP is an established and successful active surveillance program that reaches over 2500 paediatricians and paediatric sub-specialists on a monthly basis. These physicians provide care to over 7 million Canadian children and youth and are predominantly community based. In addition to the collection of data, the CPSP provides a mechanism to educate paediatricians on a monthly basis.

3 Legal Basis

3.1 Current State

The current regulatory system of product market authorization is one where the terms and conditions of market authorization (licensing) are based on the knowledge and assessment of a product’s benefit-risk prior to marketing, such as safety and effectiveness information obtained from clinical trials. The current regulatory tools are blunt instruments because they are not designed to easily respond to increasing knowledge of the real-world use of the product, such as, by changing the terms and conditions of market authorization.

Figure 1: Health Canada’s Current Health Product Review Process



For most products under the current *Food and Drugs Act*, the *Food and Drug Regulations* and the *Natural Health Products Regulations*, authorities pertaining to product vigilance, once marketed, are limited to the requirement for the MAHs to submit adverse reaction reports in specific situations and to provide annual summary reports and additional information on adverse reactions upon request by the Minister^{ix}.

For new drugs subject to Division 8, the MAHs are required to submit any new information which is significantly different from the information in the submission for authorization.

Some other vigilance tools, including the submission of Risk Management Plans (RMP), Periodic Safety Update Reports (PSUR), Development Safety Update Reports (DSUR), and look-alike sound-alike name reviews are in use; work is underway to ground these tools in regulation.

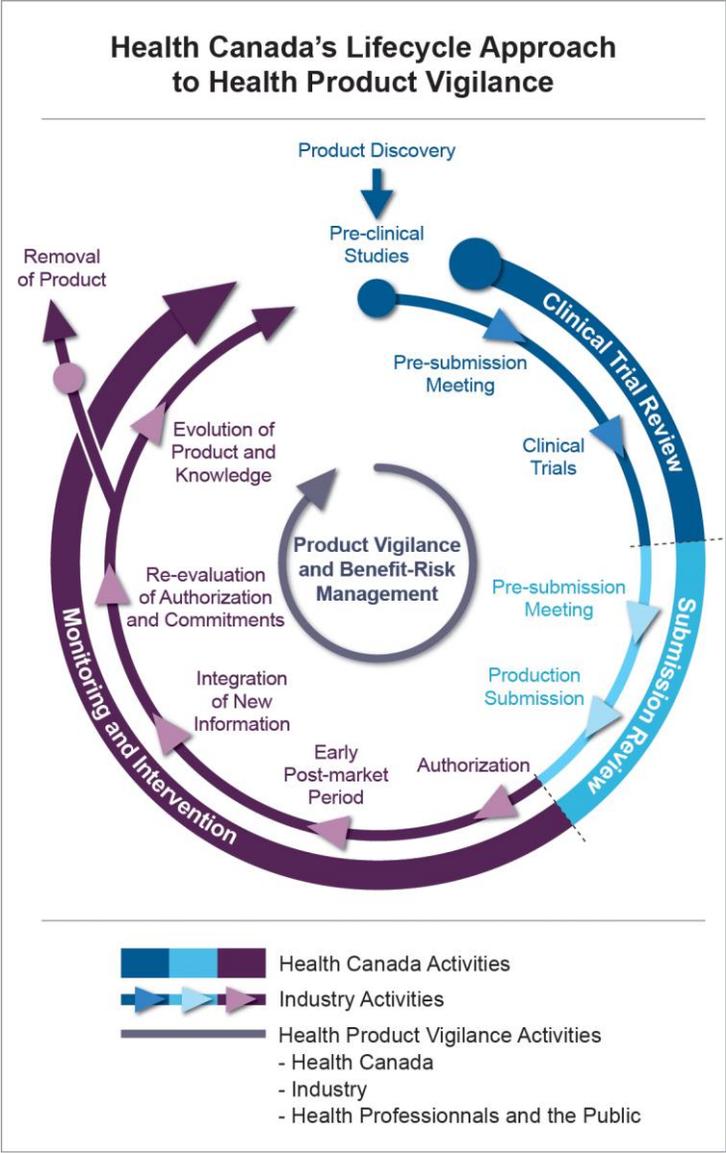
3.2 Desired State

The use of a health product over time, under real-world conditions, changes with an increased understanding of its benefit-risk. Health Canada aims to improve the integration of this knowledge by moving from the traditional point-in-time approach (Figure 1) to a product lifecycle approach (Figure 2) where what is known about the

benefit-risk of the product is assessed and applied on an ongoing basis, throughout the lifecycle of the product starting at the clinical trial stage and continuing after market authorization. The ultimate outcome of these product vigilance activities is to improve outcomes of the use and prescribing of health products over time.

Health Canada has initiated discussions with stakeholders on new legislative and regulatory instruments with the aim of providing more flexibility, consistency, continuity and accountability in the approach to regulating these products.

Figure 2: Health Canada’s Lifecycle Approach to Product Vigilance



Proposed changes to the Canadian legal framework could include:

- requiring label changes based on a re-evaluation of risk information of marketed products;
- measures to improve transparency (e.g., relating to pharmacovigilance data, assessment and decision-making and stakeholders processes such as reporting of ARs).

In this new Lifecycle Approach to Product Vigilance model, the benefit-risk of a product and its recommended uses and conditions of use could continue to be assessed based on the knowledge of the product prior to marketing and what is learned about the product while it is on the market. However, risk management and product vigilance planning could be put in place to manage the benefit-risk of a product throughout its lifecycle. For example, the benefit-risk of the product could be re-evaluated following market authorization when a new safety signal arises, after which the terms and conditions could be changed and the market authorization amended, suspended or revoked by the Minister.

Moving to this desired state of product vigilance in Canada will take time. Some innovations may depend on international developments and the introduction of new legislation to replace the current *Food and Drugs Act*. Some may depend on the creation of new regulations under the existing *Food and Drugs Act* or perhaps new innovative voluntary approaches.

Health product vigilance is a continuously evolving science and there is ongoing work to strengthen this activity moving forward. The strengthening of health product vigilance will be supported through the direct implementation of specific new actions and via developmental and supporting projects that would explore broader thematic areas in health product vigilance, to assess the opportunities, challenges, value-added and cost-benefit of specific activities, before they may be considered for implementation within existing vigilance work streams.

Strengthened health product vigilance will be distinguished by:

- **More effective and efficient surveillance practices:**
 - adopting new and emerging technologies and data sources – some current actions will be discontinued: the extent of “value-added” will be a key selection criterion in determining which actions will be implemented.
 - information/work-sharing with international counterparts.
 - focussing attention on higher-risk products/issues (eg. serious vs. non-serious adverse reaction reports).
 - adopting more “proactive” measures. Proactive vigilance methods enhance and complement those having a more passive surveillance nature. A continuum of activities, from passive to active is needed if there is to be an integrated, efficient and effective approach to health product vigilance.
 - continuing to work collaboratively with partners throughout the product life-cycle to achieve timely and effective actions.
- **Increased transparency - “telling the health product vigilance story” by:**
 - building confidence with stakeholder communities and international counterparts in communicating vigilance actions/post-market regulatory decisions taken.
 - highlighting the successes and achievements in health product vigilance.
- **Greater accountability and performance reporting – process improvements.**

4 Canada's Current Health Product Vigilance System

Canada's current product vigilance system is composed of tools that are anchored by regulations describing the responsibilities of the MAH and the Regulator for collection, analysis, and decision-making and sharing of vigilance data. This vigilance information is used when new safety information arises to re-evaluate the benefit-risk profile of marketed products and to make decisions about their continued market authorization.

4.1 Tools for the Collection and Analysis of Vigilance Data

4.1.1 Mandatory Adverse Reaction (AR) Reporting

For marketed health products, MAHs are required to submit domestic and foreign adverse reactions and also reports of unusual failure in efficacy for new drugs, pursuant to the *Food and Drug Regulations*. The success of Health Canada's reporting systems depends on the quality, completeness and accuracy of the collection and analysis of the information being submitted. Reporting of ARs and their monitoring remain viable means of identifying previously unrecognized rare or serious adverse reactions or incidents.

The following guidance documents exist for the mandatory reporting by industry of adverse reactions to Canada Vigilance: Guidance Document for Industry-Reporting Adverse Reactions to Marketed Health Products; Guidance Document for Source Establishments-Reporting Adverse Reactions to Human Cells, Tissues and Organs; and Guidance Document for Mandatory Problem Reporting of Medical Devices.

MedEffect™ Canada provides information to health professionals and consumers on the voluntary reporting of adverse reactions and medical device problem reports for all types of health products.

4.1.2 AR Reporting During Clinical Trials

During a clinical trial, whether prior to or following marketing of a product, the sponsor of a Health Canada-authorized clinical trial, is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada. This information allows timely identification of safety signals of drugs in clinical trials (whether in development or already marketed) and, aids in the identification of safety signals and the development of risk management plans.

Clinical trial sponsors are inspected to ensure the trials are conducted under good clinical practice guidelines. The inspection does not cover all trials, but only a representative sample, in line with international practices (see also the Guidance Document cited in 4.1.1 regarding Post-market Reporting Compliance inspection program).

A representative sample of clinical trial sponsors (Phase I-III Studies) are inspected to ensure the trials are conducted under good clinical practice guidelines, in line with international practices. Phase IV studies are subject to post-market AR reporting requirements and therefore are inspected under the post-market reporting compliance program.

4.1.3 Annual Summary Reporting

In accordance with the *Food and Drug Regulations*, the Market Authorization Holder is required to notify the Minister of a significant change in a product's benefit-risk profile and provide an overall safety evaluation of the product in the form of an annual summary report. If the Minister determines that an examination of the safety and/or effectiveness of a health product is/are warranted, a request can be made to furnish case reports of all adverse drug reactions and an evaluation of the product's safety profile. When such a request is made, Periodic Safety Update Reports (ICH E2C (R1)) or Periodic Benefit-Risk Evaluation Reports (ICH E2C (R2)) may be submitted to Health Canada in lieu of an Annual Summary Report.

4.1.4 Issue-related Summary Report

In accordance with the Food and Drug Regulations, the Minister may, for the purposes of assessing the safety and effectiveness of a drug, request in writing that the manufacturer submit to the Minister an issue-related summary report which shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug. The Minister shall specify a reasonable period for the submission of the report. However, the period may be shorter than 30 days if the information is required to determine whether the drug poses a serious and imminent risk to human health.

4.1.5 Risk Management Plans (RMP)

Risk management planning aims to identify safety issues early in a product's lifecycle, to develop methods to quantify and assess that risk, to put in place risk management measures that will be monitored and evaluated to determine their effectiveness in minimizing the risk, and to allow for identification of risks that may only be observed in the post-market setting.

In February 2009, Health Canada issued a notice^x regarding the two-year interim implementation of risk management planning, including the adoption of the ICH Guidance on Pharmacovigilance Planning (ICH E2E)^{xi}.

An RMP includes:

- (1) a Safety Specification, which is a summary of the known important safety information about the health product and is a means to identify gaps in knowledge;
- (2) a Pharmacovigilance Plan, which is based on the Safety Specification and identifies and characterizes known or potential safety concerns; and
- (3) a Risk Minimization Plan, which provides proposals on how to minimize any identified or potential safety risks.

Health Canada's interim implementation of risk management planning was completed in February 2011. Health Canada currently receives and reviews Risk Management Plans being submitted, on a voluntary basis by the sponsor or Market Authorization Holder. Health Canada's intent is to be harmonized with other major jurisdictions with respect to content, format and updates unless there are specificities to take into consideration related to medical practice or patients in Canada. Health Canada requests that sponsors or Market Authorization Holders submit an RMP which meets any of the following categories:

- (1) New Active Substance (NAS) (except new salts)
- (2) All biologics including subsequent entry biologics
- (3) Products withdrawn from the market due to safety concerns and the products are being re-introduced on the Canadian market
- (4) Emergent post-market safety signal
- (5) Generic products when the innovator has an RMP

4.1.6 MedEffect™ Canada Initiative

The MedEffect™ Canada Initiative was created in August 2005 to improve access to new safety information and adverse reaction reporting as well as to provide a single window approach (online, print or in person) to post-market surveillance activities and programs related to health products marketed in Canada. These products include prescription and non-prescription medications, biologics (including fractionated blood products and vaccines), natural health products, cells, tissues and organs, and radiopharmaceuticals.

In addition to addressing the requirements to make it as simple and efficient as possible for consumers, patients and health professionals to report adverse reactions, this initiative is also key for involving the public in supporting an effective post-market surveillance program. Post-market surveillance relies heavily on collaboration with external third parties and the pooling of data. These, in turn, depend upon Health Canada's solid stakeholder relations and strategic partnerships, as well as its capacity to communicate effectively to its target audiences.

4.1.7 Post-Market Regulatory Compliance (PMRC)

A limited national inspection program was put in place in 2004 to assess and verify compliance of manufacturers with the *Food and Drugs Act* and *Regulations* with regards to the regulatory requirements pertaining to reporting of adverse drug reactions and reporting of unusual failure in efficacy of new drugs to Health Canada. This inspection program applies to manufacturers of pharmaceuticals and biologics.

Health Canada is working to improve the current inspection PMRC program by examining other programs which are comparable, such as the pharmacovigilance inspection programs of the US FDA and the Medicines and Healthcare Products Regulatory Agency (MHRA).

4.1.8 Information–Bridging

Health Canada also carries out an information-bridging role by identifying other data sources that may be of use to post-market safety and effectiveness evaluations, as well as policy-related initiatives, and leverages methodological expertise from academia to enhance its in-house biostatistical analysis and review capacity.

4.2 Tools for Monitoring and Evaluating Vigilance Data

In addition to tools being used for the collection and analysis of vigilance data from clinical trials and real-world use, Health Canada uses tools for monitoring and evaluating vigilance data that is collected. These tools include the identification, prioritization, and assessment of signals that are received.

With the increased volume and variety (various degrees of severity) of signals submitted to or identified by Health Canada, a risk-based internal process has been developed for the screening and prioritizing of signals. This process allows a systematization of the risk management and the decision-making pertaining to file prioritization, provides a solid and consistent rationale for allocation of resources towards the most urgent files, and creates a record of the decisions.

The MHPD is developing a framework to monitor the AR data in the Canada Vigilance Database, in the most comprehensive manner possible and that is comparable to international partners. This framework includes:

- A method for doing routine statistical analysis (data-mining) of the Canada Vigilance Database.
- Increased transparency of the signal detection processes by developing appropriate communication documents for stakeholders.
- The development of targeted monitoring strategies for:
 - *Health product and targeted medical events (HP-TME)*: monitoring of specific health product and adverse reaction where a potential safety issue has been noted but more information is needed for confirmation;
 - *Designated Medical Events (DME)*: monitoring for reports of specific adverse reactions that are often health-product related and potentially disabling or life-threatening such as serious skin reactions or liver failure;
 - *New Active Substances (NAS)*: monitoring of health products with an active ingredient that has not been previously marketed in Canada;
 - *Special populations*: monitoring of ARs received for vulnerable populations such as children;

- *Adverse reaction reports with a fatal outcome.*

Health Canada is also the main organization responsible for monitoring the health and safety risks related to the sale and use of various health products, including drugs, as they may present different benefit-risk when used by diverse patients in post-market settings, outside the controlled environment of clinical trials. The Drug Safety and Effectiveness Network (DSEN) is being established and funded as one element under the Government of Canada's Food and Consumer Safety Action Plan. The primary objectives of DSEN are to increase available evidence on post-market drug safety and effectiveness to inform drug regulation, public reimbursement and optimal prescribing and use of drugs and to increase capacity within Canada to undertake high-quality post-market research in this area. This will be achieved by linking existing researchers in post-market drug safety and effectiveness into a virtual pan-Canadian network which will develop trusted, timely evidence to inform drug policy decisions and treatment practices. Information arising from DSEN-funded studies, along with data from other sources, will contribute to the assessment of real-world drug safety and effectiveness.

4.3 Reporting on Vigilance Activities

Health Canada reports on the monitoring and evaluation of information related to the safety and efficacy of marketed health products through a variety of means. Under its umbrella, the MedEffect™ Canada Initiative offers consumers, health professionals and industry a variety of programs, services and products including reports of the post-market surveillance program. Examples of sources of information include:

- Advisories & Recalls that give Canadians timely new safety information on health products as it becomes available.
- The Canada Vigilance Adverse Reaction Online Database which permits Canadians to view adverse reaction reports submitted to Health Canada.
- The Canadian Adverse Reaction Newsletter (CARN), featuring articles and data related to serious or unexpected adverse reactions that are suspected of being associated with marketed health products in Canada.
- The Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP), a component of the post-market surveillance program, represents patients and consumers, health and industry sectors, researchers and academics and provides broad strategic policy advice on the safety and therapeutic effectiveness of marketed health products.
- Consultations to gather varied input that will shape decisions about the safety, effectiveness and access to marketed health products available to Canadians.
- Reports and other publications related to reporting adverse reactions, obtaining new safety information on marketed health products, and other information related to risk communications.

International cooperation is supported by memoranda of understandings with key international regulators which enable sharing of vigilance data on a bilateral basis. As well, Health Canada shares vigilance data with provincial/territorial governments and with non-government partners.

5 Proposed Model for Health Product Vigilance in Canada

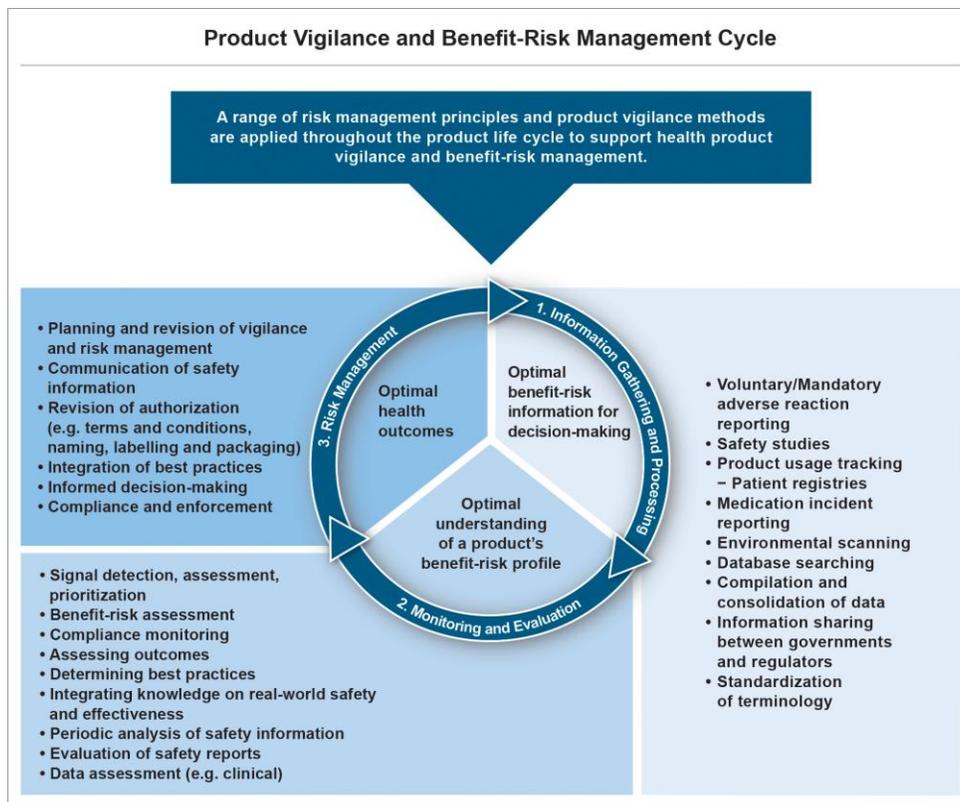
The future of Canada’s product vigilance system will build on our current system of collection, analysis, decision-making and sharing of vigilance data. Active surveillance and other forms of proactive vigilance will support decision-making by providing information that is more opportune, more complete and of better quality. The product vigilance system will consist of an integrated set of product vigilance tools that will work together to protect the health and safety of Canadians.

The Product Vigilance Model proposed by Health Canada consists of the continuous integration of new product vigilance tools into the three functions, which occur throughout the product lifecycle, associated with Health Product Vigilance, namely information gathering and processing, monitoring and evaluation and risk management. Vigilance tools will be implemented in a step-wise approach, beginning with those applied to higher risk pharmaceuticals and biologics. New vigilance tools may be added in the future as the field of vigilance evolves.

It has been suggested that the application of the product tools be based on the risk level of the product type. As shown in Figure 3, the functions associated with Health Product Vigilance occur, in theory, throughout the product lifecycle to support the reassessment of the benefit-risk profile of marketed health products.

While working towards the integration of new tools into the Vigilance Model, new or improved regulations, guidelines, and/or policies will need to be developed to update the legal framework. In addition, new or re-engineered processes as well as new Information Management and Information Technology (IM/IT) tools will be implemented within Health Canada to support the new product vigilance model.

Figure 3: Diagram of “Product Vigilance and Benefit-Risk Management Cycle”



5.1 Product Vigilance Tools

Product vigilance tools are defined by the World Health Organization as tools used to detect, assess, understand or prevent adverse events or any other health product-related problems. For the purpose of this framework, product vigilance tools are defined as tools designed to facilitate the collection and evaluation of information pertaining to the benefit-risk associated with the use of health products. A description of the product vigilance tools in use or in development are found in Table 1.

Table 1: Description of Product Vigilance Tools

Health Product Vigilance (PV) Tool	Description of Method	Product Lines affected now or within 3-5 years	Primary Source of Information
Adverse Reaction (AR) Reporting	<ul style="list-style-type: none"> • Reports on noxious and unintended responses to drugs in clinical trials or marketed in Canada. • Expedited reporting of serious unexpected clinical trials adverse drug reactions occurring inside or outside Canada. • Reports on failures, deterioration, etc. of medical devices. 	<ul style="list-style-type: none"> • Pharmaceuticals (including self-care products); • Biologics; • Radiopharmaceutical drugs; • Natural Health Products • Radiopharmaceuticals; and • Medical Devices 	<ul style="list-style-type: none"> • MAH • Health professionals • Patients and consumers • Clinical trial sponsors
Risk Management Plan (RMP)	<ul style="list-style-type: none"> • Summary of the known important safety information about the health product (safety specifications); • Plans to identify and characterize known or potential safety concerns (pharmacovigilance plan) and to minimize any identified or potential safety risk (risk minimization plan). 	Products for human use including: <ul style="list-style-type: none"> • Pharmaceuticals; • Biologics; and • Radiopharmaceuticals 	MAH
Periodic Safety Update Report (PSUR)	<ul style="list-style-type: none"> • A periodic comprehensive assessment of the world wide safety data of a marketed health product. 	Products for human use including: <ul style="list-style-type: none"> • Pharmaceuticals; • Biologics; and • Radiopharmaceuticals 	MAH

Medication Incident Management Approach (MIMA)	<ul style="list-style-type: none"> Information on product naming, packaging and labelling; and collecting and analysis Medication Incident Data 	Products for human use including: <ul style="list-style-type: none"> Pharmaceuticals (including self-care products); Biologics Natural health products 	<ul style="list-style-type: none"> Industry Patient safety organizations Health professionals
Canadian Medical Devices Sentinel Network (CMDSNet)	<ul style="list-style-type: none"> Reports from health institutions on adverse events associated with medical devices. A Sentinel System 	<ul style="list-style-type: none"> Medical devices Device and drug combination products 	Health professionals from Canadian acute or community based health care facilities.
Drug Safety & Effectiveness Network (DSEN)	Real-world drug safety and effectiveness evidence, including post-market studies.	Products for human use including: <ul style="list-style-type: none"> Pharmaceuticals Biologics Radiopharmaceuticals 	Academia
Environmental scanning	Collection and review of scientific and medical literature, media reports and regulatory news for monitoring and evaluation.	All product lines	<ul style="list-style-type: none"> Media Academia Governments Industry Consumers
Development safety update reports (DSUR)	A periodic review and evaluation of safety information collected during the development period of a health product. (Clinical Trial)	Products for human use including: <ul style="list-style-type: none"> Pharmaceuticals Biologics 	Industry

Integrating new product vigilance tools into the business functions of Health Canada will require the proactive modification of some processes and the creation of others. The main processes required for each PV tool include:

- receipt of information sent to Health Canada (as well as for the collection of information that Health Canada seeks);
- transmission of this information to the appropriate organizational area;
- screening and/or prioritization of the information received; and
- review/evaluation of the report or information.

When deciding on the integration of new product vigilance tools, Health Canada will proactively involve stakeholders and partners in a transparent and participative process, and decisions will be made on a value-added or priority basis.

5.2 Prioritization Schemes

To use resources efficiently and effectively, Health Canada chooses to focus on those products and activities that pose greater risks to Canadians. Resources are spent to maximize benefit and to minimize the risk to Canadians. The level of risk posed by the product determines which tools are used and how they are used. As outlined in Table 2, there may be different requirements for a new product where we have limited information for real world usage. The different product vigilance tools use prioritization schemes as guides for the request and processing of

safety and effectiveness information submitted to or gathered by Health Canada. These schemes, found in the Table below, follow a risk-based and flexible approach which considers operational priorities within Health Canada.

Table 2: Product Vigilance Tool Prioritization Schemes

Health Product Vigilance (PV) Tool	Description of prioritization scheme	Comment
Adverse Reaction (AR) Reporting	AR reports are screened and sent into either a regular or a priority workflow stream.	All AR reports follow an electronic workflow process with priority reports having the most stringent performance standards. For drugs in development, critical AR reports can trigger immediate discussions with clinical trial sponsors re; impact on subject safety, clinical trial design and/or labelling
Risk Management Plan (RMP)	Proposed prioritization is based on levels of risk or uncertainty –products we know little about (high level of uncertainty) and those that are known to have significant risk. In general, these products will require an RMP.	<ul style="list-style-type: none"> • Prioritization scheme is in development. • RMP interim implementation will inform the prioritization scheme.
Periodic Safety Update Report (PSUR)	Proposed prioritization is based on levels of risk or uncertainty – products we know little about (high level of uncertainty) and those that are known to have significant risk	<ul style="list-style-type: none"> • Prioritization scheme will align with RMP. • Higher risks could result in more frequent reporting.
Medical Incident Management Approach (MIMA)	Prioritization scheme will follow that of the already defined and used National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) Index for Categorizing Medication Errors.	Prioritization scheme and workflow process is in development.
CMDSNet	Prioritization scheme follows the risk categories already defined for medical devices in the Human Health Evaluation Guideline.	CMDSNet Pilot is following this prioritization; however, at this time all reports are being reviewed and evaluated.

5.3 Benefit-Risk Assessment

Product vigilance evaluation involves the ongoing assessment of the benefit-risk of a product (including data from adverse reaction reports, clinical trials, meta-analysis, observational studies, etc.) and the assurance that benefits outweigh the risks for a given population during clinical trials and following its market authorization. Currently, Health Canada is developing a Branch approach to a benefit-risk assessment model, in consultation with international regulators.

Benefit-risk assessment is an important regulatory tool that highlights the benefit-risk of therapeutic products. Industry (market authorization holder) is primarily responsible for developing benefit-risk assessments. Health Canada’s responsibility is to evaluate these documents and other relevant information when a change in the

product's benefit-risk profile is identified, which is referred to as a "benefit-risk assessment review".

A benefit-risk assessment of a therapeutic health product is requested when the benefit-risk profile of a product has changed. Health Canada evaluators reviewing benefit-risk assessments currently use science-based procedures to determine whether the benefits outweigh the risks or whether the product needs regulatory intervention. With the current regulatory landscape, these interventions generally fall within the following options:

1. Issuance of a risk communication;
2. Revision of market authorization (e.g., terms and conditions, naming, labelling & packaging);
3. Further investigation by the regulator; and/or
4. Enforcement of regulations such as stop sale.

Although Health Canada uses both qualitative and quantitative methodologies when performing benefit-risk assessment reviews, collaborative efforts with international stakeholders such as the Report of the Council for International Organizations of Medical Sciences (CIOMS) are underway to refine these methodologies. The results of these talks will need to be tested and refined before introduction into the benefit-risk assessment review process may occur.

5.4 Practical Aspects of the Product Vigilance System

Health Canada is aware of the international product vigilance landscape and takes into consideration the best practices on various aspects of an integrated product vigilance system. Although it is important to align as much as possible with international product vigilance best practices, Canada will have to consider the impacts on safety, as well as the administrative burden on both the MAH and the Regulator when deciding on steps forward for implementing product vigilance requirements.

6 The Future

This is a time of positive and stimulating change – to be proactive as we strive to make our work more transformative, value-added and in harmonization with our colleagues abroad. To accomplish this, we will respond to new challenges while building on our successes and managing our priorities so that these objectives can be achieved. We will also communicate progress on the development of the vigilance tools internally and externally so that Canadians understand how the work of the tools fit together. As we strive to achieve the Framework’s vision, we will adhere to Health Canada’s core values^{xiii} and legislative mandate, while at the same time responding to challenges that are increasingly complex.

Annex 1: Guiding Principles

The guiding principles described below reflect Health Canada's product vigilance philosophy. These principles are interrelated and will be applied to the Health Product Vigilance Framework.

1. Adopt a product lifecycle approach

It is well recognized that product vigilance needs to occur throughout a product's lifecycle. This Health Product Vigilance Framework will consider vigilance as it relates to the entire product lifecycle and will require regulatory change for some elements. Regulatory agencies around the world are building on the strengths of the pre-market review and moving to a lifecycle approach to regulating health products that takes into account the entire body of evidence that accumulates throughout the lifecycle of the product, and have enacted the necessary legislation to support this shift.

2. Align with international best practices and standards

Health Canada has committed to aligning its regulatory approaches related to product vigilance, wherever possible, with those of comparable international regulatory counterparts. This includes a commitment to full integration of ICH vigilance tools and provides the vehicle through which international work and information sharing can proceed.

3. Facilitate industry compliance with vigilance best practices

Through the development of this framework, Health Canada will provide regulated parties with the tools needed to follow vigilance best practices. This will include an explanation of the various vigilance tools, when they are used, and appropriate guidance to facilitate compliance with the tools.

4. Align with Health Canada's Decision-Making Framework

Product Vigilance activities are guided by the *Health Canada Decision-Making Framework*^{xiii}, three key components being transparency and timely decision-making, use of precautionary approach, and meaningful public involvement.

5. Continuously improve product vigilance

Health Canada recognizes that product vigilance activities may change over time as knowledge of a product evolves. A product's vigilance requirements should be subject to review over a product's lifecycle, on the basis of the evolution of knowledge, technology and society's chosen level of protection. Also, vigilance tools will be evaluated for effectiveness in carrying out their desired purposes.

6. Uphold product efficacy and safety standards

The requirement for specific vigilance activities will be for the purpose of protecting the health and safety of Canadians and will in no way result in the reduction in a product's requisite efficacy and safety standards.

7. Use of Foreign Reviews in the Regulatory Review of Health Products

Foreign reviews are scientific safety, efficacy, and quality reports prepared by foreign regulatory authorities, upon which the decisions on marketing authorization are based. When available, foreign reviews should be considered for all applications/submissions for human and veterinary biologicals (except veterinary vaccines), radiopharmaceuticals, pharmaceuticals and medical devices. The extent of use of foreign reviews will be determined and guided by a benefit-risk assessment of using the reviews to inform the regulatory decision-making process.

Annex 2: Acronyms

AR	Adverse Reaction
CMDSNet	Canadian Medical Devices Sentinel Network
DSEN	Drug Safety and Effectiveness Network
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
HPFB	Health Products and Food Branch
ICH	International Conference on Harmonisation
IM/IT	Information Management and Information Technology
MAH	Market Authorization Holder
MHPD	Marketed Health Products Directorate
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMA	Medication Incident Management Approach
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
PDUFA IV	Prescription Drug User Fee Act
PMRC	Post-Market Regulatory Compliance
PSUR	Periodic Safety Update Report
PV	Product Vigilance
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
TGA	Therapeutic Goods Administration
YBPR	Yearly Biologics Product Report

Annex 3: Endnotes and References

ⁱ *Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food*; <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/index-eng.php>

ⁱⁱ *Health Canada: The Food and Consumer Safety Action Plan*; <http://www.hc-sc.gc.ca/ahc-asc/activit/strateg/fcsap-paaspac-eng.php>

ⁱⁱⁱ *Planning for Our Future: Federal Regulatory Post-Market Surveillance Strategy 2007-2012*; http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/strategy_strategie_surveillance-eng.php

^{iv} *Regulation (EU) No.1235/2010 of the European Parliament and of the Council of 15 December 2010*; <http://eur-lex.europa.eu/lexuriserv/lexuriserv.do?uri=oj:l:2010:348:0001:0016:en:pdf>

^v *Food and Drug Administration Amendments Act (FDAAA) of 2007*; <http://www.fda.gov/oc/initiatives/advance/fdaaa.html>

^{vi} *Prescription Drug User Fee Act (PDUFA)*; <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

^{vii} *Australian Government, Department of Health and Ageing, Therapeutic Goods Administration (TGA), Legislation & legislative instruments*; <http://www.tga.gov.au/industry/legislation.htm>

^{viii} *Food and Drug Regulations, Part C, Division 1, Adverse Reaction Reporting (C.01.016), C.R.C., c. 870; Food and Drug Regulations, Part C, Division 8, New Drugs (C.08.007, C.08.008), C.R.C., c. 870; Natural Health Products Regulations, Section 24, Reaction Reporting, C.R.C., SOR/2003-196.*

^{ix} *Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E*; http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php

^x *International Conference on Harmonisation (ICH); Newsroom* - <http://www.ich.org/ichnews/newsroom.html>

^{xi} *Product Vigilance*; <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/index-eng.php>

^{xii} *Health Canada – Core Values*; <http://www.hc-sc.gc.ca/ahc-asc/activit/about-apropos/index-eng.php#val>

^{xiii} *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000*; http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php