Innovation in Signal Detection, Risk Assessment and Risk Management for Patient Safety on the Perspective of the Network Partners in Post-Market Surveillance in Canada

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Purpose

To provide an overview of:

- The current state of Canadian post-market regulation and pharmacovigilance.
- The Protecting Canadians from Unsafe Drugs Act and the Regulatory Modernization.
- Canadian pharmacovigilance experience working with networks.
Health Canada is the Federal department responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances.
Health Canada’s Mission and Vision

Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.
Health Product and Food Branch’s Mandate

- The Health Products and Food Branch (HPFB)'s mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:
  - minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food;
  - promoting conditions that enable Canadians to make healthy choices and providing information to make informed decisions about their health.
Marketed Health Products Directorate (MHPD)

- Responsible for:
  - Collecting Adverse Reactions (AR) Reports
  - Detecting, assessing and managing potential safety concerns (signals)
  - Issuing risk communications
  - Recommending label changes
  - Evaluating risk management plans
MHPD Offices and Bureaus

Biologics, including:
- vaccines
- blood and blood products
- cells, tissues and organs
- biotechnology products.

- natural health products
- non-prescription drugs.

- investigates safety-risks
- evaluates Risk Management Plans
- reviews benefit-risk balance

• real world evidence for decision making
• drug utilization

• human resources
• finances
• planning & reporting
• stakeholder engagement & communication

• Risk communications
• patient safety
Key Partners:
Biologics and Genetic Therapies Directorate
Therapeutic Products Directorate
Natural and Non-Prescription Drugs Health Products Directorate

- Responsible for:
  - Pre-market review and market authorization
  - Regulatory policy development
  - Issuing Guidance Documents
  - Health Risk Assessments
Regulatory Authorities

Food and Drugs Act

• Provides a framework for the oversight of the safety and effectiveness of food and drugs.

• Gives the Minister power to conduct inspections, limit advertising, and make and enforce regulations on the safety and effectiveness of regulated products.
Food and Drugs Act

• Food and Drug Regulations (Part C – Drugs)
  – Division 4 (Vaccines, blood products, insulin)
  – Division 8 (New Drugs)
  – Division 1 (General)

• Safety of Human Cells, Tissues and Organs for Transplantation Regulations
  – Sections 47, 48, 51 and 54 (Adverse reaction assessment and reporting)

• Blood Regulations
  – Sections 110-116 (Adverse reaction investigation and reporting)

• Natural Health Products Regulations
  – Sections 24 (Adverse reaction reporting and annual summary report preparation)
Serious adverse reaction reporting (C.01.017)

Manufacturers are required by law to report serious ARs

C.01.017 of the Food and Drug Regulations reads as follows:

“The manufacturer shall submit to the Minister a report of all information relating to the following serious adverse drug reactions within 15 days after receiving or becoming aware of the information, whichever occurs first:

(a) any serious ADR that has occurred in Canada with respect to the drug; and

(b) any serious unexpected ADR that has occurred outside Canada with respect to the drug.”
Serious adverse reaction (ADRs) reporting (C.01.017)

• Although reporting of non-serious ARs is not a regulatory requirement, this practise is encouraged for biologic products, as clusters of non-serious ARs may highlight potentially serious lot issues, which fall under the scope of our surveillance activities.

• Consumers and Health Care Practitioners also report serious and non-serious ARs on a voluntary basis.

• ARs “side-effects” can be reported by:
  – Fax/Telephone: 1-866-234-2345
  – Mail: Canada Vigilance Program
  – Online: canada.ca/medeffect
Annual safety summary reports (C.01.018)
Periodic Safety Update Report (PSUR)/
Periodic Benefit Risk Evaluation Report (PBRER)

C.01.018 of the Food and Drug Regulations reads as follows:

“The manufacturer shall prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drug reactions to the drug that it received or became aware of during the previous 12 months.”

It should contain:

• critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug; and

• significant change in what is known about the risks and benefits of the drug during the period covered by the report.
Issue-Related Summary Report (C.01.019)

C.01.019 of the Food and Drug Regulations reads as follows:

“The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister an issue-related summary report.”

It should contain:

• a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug;
• case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known in respect of the issue; and
• significant change in what is known about the risks and benefits of the drug during the period covered by the report.
Benefit-Risk (C.01.013)

C.01.013 of the Food and Drug Regulations reads as follows:

“Where the manufacturer of a drug is requested in writing by the Minister to submit on or before a specified day evidence with respect to a drug, the manufacturer shall make no further sales of that drug after that day unless he has submitted the evidence requested.”

“If a manufacturer is notified that the evidence with respect to a drug is not sufficient, he shall make no further sales of that drug unless he submits further evidence and is notified in writing by the Minister that that further evidence is sufficient.”
Signal Detection

• **Active information sharing with other regulators**
  – Regular *International Post-market Surveillance Group* teleconference: Australia, Canada, New Zealand, USA, Singapore, Switzerland, United Kingdom
  – Communications from foreign agencies (early warnings, risk communications, safety updates, newsletters, observer status at EMA PRAC etc.)

• **Environmental Scanning**
  – Scientific literature
  – Public safety communications from other regulators

• **Adverse reaction reporting from Canadians**
  – Canada Vigilance Program invites consumers, healthcare professionals and others to report events directly to Health Canada – online, mail, fax, phone.

• **Information and reports received from manufacturers**
  – Adverse reaction reports
  – PSURs and PBRERs
  – Information from safety studies/registries
Post-market Safety Surveillance within MHPD

Information Sources

- Scanning
  - Media
  - Medical and scientific literature

- International Regulatory Agencies
  - Databases
  - Warnings/Advisories

- Manufacturer
  - Phase IV studies
  - PSURs
  - Registries

- Health Canada
  - Canada Vigilance
  - WHO-Vigimed
  - Pre-market safety information
  - Drug Safety and Effectiveness Network

Regulatory Actions

- Increased Monitoring
- Product Labelling Changes
- Withdrawal or Market Authorization
- Regulatory Interventions
- Product Advertising Changes or withdrawal

Risk Communication

- Health Care Professionals:
  - Dear Health Care Professional(s) Letter

- Health Canada Web site:
  - Summary Safety Review
  - Advisory
  - Recall
Improving Our Legislation
Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law)

• Vanessa’s Law, which received royal assent in 2014, was the first significant change to the *Food and Drugs Act* since the 1950s.

• Vanessa's Law achieves the following:
  ✓ provides a range of pre- and post-market regulatory tools that enable the safety oversight of therapeutic products throughout their lifecycle;
  ✓ improves reporting by certain health care institutions of serious adverse drug reactions and medical device incidents involving therapeutic products (once regulations are in place);
  ✓ promotes greater confidence in the oversight of therapeutic products by increasing transparency; and
  ✓ better aligns with the US, Australia, and European Union regulatory counterparts.
Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law)

- The Act was written 50 years ago – when the focus of drug regulations was around pre-market safety (ensuring when the drug went on the market it was safe).
Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law)

- Today, the world is shifting to a lifecycle approach that also includes post-market safety (ensuring the drug stays safe once it’s on the market).
Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law)

This Law enables the Government to:

- Require **strong surveillance**, including mandatory adverse drug reaction reporting by healthcare institutions;

- **Recall** unsafe therapeutic products;

- **Impose tough new penalties for unsafe products**, including jail time and new fines of up to $5 million per day instead of the current $5,000;

- Provide the courts with discretion to impose **even stronger fines** if violations were caused intentionally;

- Require drug companies to **revise labels to** clearly reflect health risk information, including potential updates for health warnings for children; and

- Require drug companies to do **further testing on a product**, including when issues are identified with certain at-risk populations such as children.
New regulations linked to Vanessa’s Law to further Strengthen the Safety and Surveillance of Drugs and Medical Devices

• The proposed regulations will improve the **reporting of serious adverse drug reactions** and **medical device incidents** by **hospitals**.

• The reporting of adverse events provides direct information about the real-world experiences of patients and health care professionals using these products. These reports are an important source of post-market drug and device safety information for regulators worldwide.

• Under the proposed regulations, which are currently undergoing an external consultation, hospitals will be required to report to Health Canada all serious adverse drug reactions and medical device incidents, **in writing, within 30 days** of when the incident was first documented within the hospital.

• The proposed regulations aim to improve the quality and increase the quantity of serious adverse drug reaction and medical device incident reports provided to Health Canada.
Modernizing our Regulatory Landscape
Regulatory Review of Drugs and Devices in Canada “R2 D2”
R2 D2 Drivers for Change

In order to meet the changing needs of Canadians, we are modernizing our regulatory landscape in response to a number of trends:

- Increasing complexity of products: new therapeutic products are treating niche conditions, involve complex biologic organisms, and use new combinations of devices and drugs.

- Growing demand to consider healthcare system needs in reviews: there is currently no mechanism to consider healthcare system needs when granting priority review status.

- Timing of system reviews cause lags: Drugs undergo various reviews before they are covered by Federal/Provincial/Territorial (F/P/T) drug plans (Health Canada review of safety, efficacy and quality, followed by health technology assessment at the Canadian Agency for Drugs and Technologies in Health (CADTH), then F/P/T formulary listing decisions) – This delays access for Canadians who may benefit from receiving early access to new treatments.

- Heavy reliance on pre-market information: limited use of “real world” post-market evidence in our decision-making.
Health Canada’s Regulatory Review of Drugs and Devices

- **Objective:** An agile regulatory system that supports better availability of therapeutic products based on healthcare system needs

**Expanded collaboration with health partners**
- Alignment of the Health Technology Assessment (CADTH) Review with Health Canada Review
- Implementing a Mechanism for Early Parallel Scientific Advice
- Use of Foreign Reviews/Decisions
- International Collaboration and Work Sharing in Reviews

**More timely availability of drugs and devices**
- Expansion of Priority Review Pathways
- Improving Availability of Biosimilars and Biologics
- Improving Availability of Generic Drugs
- Building Better to Digital Health Technologies
- Pre-Submission Scientific Advice for Medical Devices
- Special Access Programme (SAP) Renewal

**Enhanced Use of real-world evidence**
- Leveraging Data for Assessing Drug Safety and Effectiveness
- Strengthening Post-market Surveillance of Medical Devices

**Modern and flexible operations**
- Updated System Infrastructure
- Appropriate cost recovery framework
- Public Release of Clinical Information
R2 D2 Plan: More timely access to drugs and devices, including orphan drugs / drugs for rare diseases

- Expanding the priority review process, to decrease review time for products needed by the health care system, including drugs for rare diseases.

- Renewing the Special Access Programme to improve access to products that are not now authorized for sale in Canada.

- Improving access to generics, biosimilar drugs and biologics by ensuring more timely review of these products.

- Building better access to digital health technologies for home use (such as remote monitoring devices) and expediting these applications.

- Formalizing pre-submission scientific advice for the medical devices industry to define specific review requirements.

- Better use of real-world evidence to support regulatory decisions across a product's life cycle for both drugs and medical devices.
Work Sharing and Collaboration
Within Canada and Internationally
Vaccine Safety Surveillance
Vaccine Safety Surveillance

- In Canada, Vaccine Safety Surveillance is a *shared activity of regulatory branches* and *public health* (Provinces and Territories).

- **BGTD and MHPD** are responsible for regulatory activities involving manufacturers.

- **PHAC** is responsible for monitoring infectious diseases, supporting immunization programs, and monitoring the effectiveness and safety of vaccines administered in publicly funded programs.
Vaccines:

Reporting of Adverse Events Following Immunization (AEFI) in Canada
Real World Evidence: Drug Safety and Effectiveness Network DSEN

Since 2009
DSEN is a network of real-world drug safety and effectiveness researchers coordinated through the Canadian Institutes of Health Research and Health Canada.

One of its objectives is to respond to drug safety and effectiveness queries from federal and provincial decision-makers and thus make a contribution to a Canadian marketplace with safe and effective drugs.

DSEN supports a product life-cycle approach to drug regulation by providing additional evidence for use in ongoing risk-benefit assessment and an additional tool for surveillance.
The Drug Safety and Effectiveness Network-DSEN

Allows a pan-Canadian approach to research

• **Facilitates** interaction between researchers and decision makers - integrated knowledge translation.

• **Coordinates** a national agenda of research, based on priorities identified by decision/policy makers – improve relevance and utility of research.

• **Leverages** greater value from existing investments in post-market drug safety & effectiveness research
• Increase the evidence on the post-market safety and effectiveness of drugs available to public drug plan managers, policy-makers, health technology assessors, regulators and other end-users, to support their decision making.

• Increase the capacity within Canada to undertake high-quality post-market research in this area.

• Provide *Professional Development in Pharmacoepidemiology*. DSEN coordinated a series of ten lectures in pharmacoepidemiology, open to Health Canada employees. Courses taught by senior scientists and researchers from across Canada.
DSEN - Partners

- **Health Canada Branch Partners**
  - Policy and regulatory directorates across four branches

- **Federal Health Portfolio Partners**
  - Public Health Agency of Canada
  - Canadian Institutes of Health Research
  - Patented Medicine Prices Review Board

- **Provincial and Territorial Governments**
  - Manage drug formularies, practice of medicine/pharmacy, regulate health professionals, deliver health care services

- **Common Drug Review** (via Canadian Agency for Drugs and Technologies in Health)

- **International Organizations and Regulatory Counterparts**
The Drug Safety and Effectiveness Network (DSEN)

Regional Distribution of Researchers

- Ontario: 33%
- Québec: 17%
- Atlantic Provinces: 7%
- National org.: 4%
- British Columbia: 17%
- Alberta: 7%
- Saskatchewan: 3%
- Manitoba: 7%
- Outside Canada: 5%
Some Examples of Queries Successfully Completed

Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data

Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy

Antidepressant use and 10-year incident fracture risk: the population-based Canadian Multicentre Osteoporosis Study (CaMoS)
Life Cycle Approach

Sophie, I am including these 2 slides to close the idea about life cycle approach and the integration of real world data.
International Collaboration
Health Canada - United States Food and Drug Administration

- Health Canada and the U.S. Food and Drug Administration continue to work closely together to **harmonize and align their pre and post-marketing surveillance requirements and standards** (including pharmacovigilance issues) for pharmaceuticals and biologics.

- Regulators continue to **share inspection schedules bilaterally and through the Pharmaceutical Inspection Co-operation Scheme** and to promote leveraging of inspectional resources to maximize inspection coverage.

- **Common Electronic Submissions Gateway:** This is cooperative agreement to share technology that make it more efficient for industry to submit applications to both the U.S. and Canada for the approval of pharmaceutical and biological products; the common infrastructure enables industry to submit to both countries using the same electronic format for technical documents.
Health Canada-EMA: Confidentiality arrangement

Since 2007, the EMA and Health Canada have agreed to share confidential info with each other, including:

- All legislation and guidance documents.
- Post-authorisation pharmacovigilance data, adverse drug reactions, safety concerns arising from periodic safety update reports and post-authorisation obligations and commitments.
- Applications for scientific advice, orphan designation, marketing authorisation or post-authorisation activities of significant public health interest.
- Applications for agreement of pediatric investigation plans.
- Good-clinical-practice (GCP) inspections for specific products and GCP inspection reports available to EMA or the European Commission.
- Information technology systems supporting regulatory processes.
- Health Canada is a visiting national expert at the EMA Pharmacovigilance Risk Assessment Committee “PRAC” Meetings.
Australia Canada Singapore Switzerland

... a truly global network!
Effective Information and Work-Sharing

• The ACSS Consortium was formed in 2007 to explore opportunities for work-sharing between like-minded medium-sized regulatory authorities.

• Basis: Network of bilateral agreements/arrangements between the four agencies.

• Voluntary network to build synergies, enhance effectiveness and efficiency of domestic regulatory systems and capitalize on each country’s area of strength.

• Working Groups, e.g. Information Technology is chaired by HC, New Chemical Entities and Benefit-Harm-Risk is co-chaired by HC and TGA.
Australia Canada Singapore Switzerland (ACSS) Consortium
Erleada approval (Canada-Australia Joint Review)

• On July 4, 2018 Health Canada approved the first drug to be evaluated under the Australia-Canada-Singapore-Switzerland (ACSS) Consortium’s New Chemical Entities Work Sharing Trial.

• The Work Sharing Trial is an initiative under the “Regulatory Review of Drugs and Devices” and is aimed at strengthening our international partnerships in submission review and enabling a prompt authorization of the drug product to allow Canadians to have faster access to the medicines they need.

• Each regulator evaluated their respective country-specific information and clinical data, while HC (Canada) evaluated the quality data and the TGA (Australia) evaluated the toxicology data.

• The potential gains from this initiative include a reduction in regulatory burden (e.g., with the filing of common dossiers), the potential for similar market authorisation dates between regions and consolidated questions to applicants.

International Post-market Surveillance Group

A network that facilitates the exchange of information about the safety of marketed drug products.

Members:

- **Canada**: Health Canada, Health Products and Food Branch
- **Australia**: Commonwealth Department of Health, Therapeutic Goods Administration, Post-marketing Surveillance Branch
- **New Zealand**: Ministry of Health, Medsafe
- **USA**: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, with the participation of the Center for Biologics Evaluation and Research and the Center for Food Safety and Applied Nutrition
- **Singapore**: Health Sciences Authority, Health Products Regulations Group
- **Switzerland**: Pharmacovigilance Unit, Swissmedic
- **United Kingdom**: Medicines and Healthcare Products Regulatory Agency (MHRA)

- **Bi-monthly** meetings
- **Each participating country** identifies issues of interest, and other countries provide information (confidential).
International Council for Harmonisation (ICH)

• Since October 23, 2015 Health Canada is an **official member** to the new ICH association.

• Health Canada is committed to the adoption and implementation of ICH guidances.

• Unique harmonisation initiative between regulators and pharmaceutical industry that develops technical guidelines for the regulation of pharmaceuticals for human use.

• As part of the regulatory cooperation initiative, **Health Canada and FDA host a Joint Public Consultation**; on International Council for Harmonisation (ICH) Guidelines prior to each ICH meeting (most recently on April 6, 2018).
The Group of National Regulatory Authorities of Regional Reference (NRAr) in the PAHO Region
Canada – PAHO cooperation

**Background:** The VII Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) was held in Ottawa in collaboration with Health Canada in September 2013: *Sixteen Years Promoting Good Regulatory Practices in the Region of the Americas.*

**Joint Evaluation of PSURs and RMPs**

- **Rational:** Pharmacovigilance in the Americas presents major challenges in terms of operations and communications.

- **Needs:** Integration of Regulatory Authorities to minimize workload. Knowledge transfer.

- **Opportunities for Regulatory Convergence:** The project permits the exchange and use of information generated among the NRAs in order to help close a gap that affects most of the countries, with potential for great impact on the safe use of medicines in the health systems.
Conclusions

- The discipline of pharmacovigilance has developed considerably and it remains a dynamic clinical and scientific discipline.

- It has been essential to meet the challenges of the increasing range and potency of medicines (e.g. new biologics and biosimilars), which carry with them an inevitable and sometimes unpredictable potential for harm.

- Working on networks in the area of the Pharmacovigilance provides opportunities to maximise resources and increase knowledge on the safety and effectiveness of pharmaceuticals when used by diverse patient populations outside of the controlled experimental environment of clinical trials.
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