



Health  
Canada

Santé  
Canada

*Your health and  
safety...our priority.*

*Votre santé et votre  
sécurité...notre priorité.*

# Canada Vigilance

## Adverse Reaction Monitoring Program and Database

Network of Rare Blood Disorder Organizations

Friday November 13, 2009

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Director

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Marketed Health Products Directorate

Health Canada



MedEffect Canada

*Together we can improve  
health product safety*

MedEffet Canada

*Ensemble nous pouvons améliorer  
l'innocuité des produits de santé*

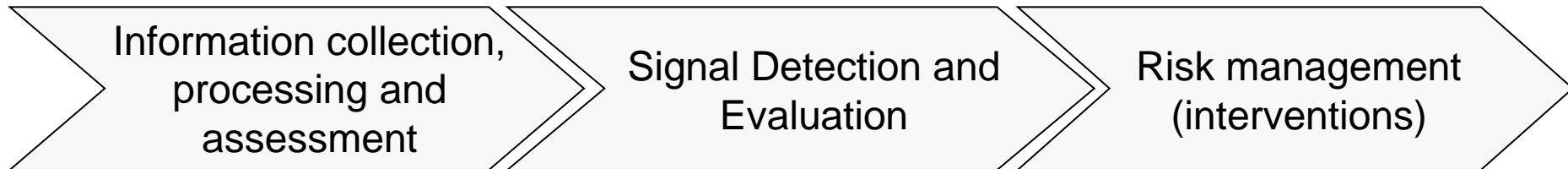
Canada 

## Objective

- MedEffect™ Canada/Canada Vigilance Program and Database
- Data Management and Standards
- Privacy



# Post-market surveillance is composed of three major activities:



Adverse events occur and information is gathered. Reports are assessed for completeness and assigned medical terminology. Data entry into computer system. New risks are discovered with increased use of product in real world. Information is compiled from literature scan, other regulatory agencies, companies (PSURs, registries, clinical trials), etc.

Many information sources combine to create a signal: a suspicion there is a connection between a product and reported adverse reactions. Evaluation consists in the scientific/medical review of multiple data sources to analyse risks and benefits, considering risk profiles of therapeutic alternatives.

A risk management approach is defined which may include interventions such as: product recall, labelling changes, communicating risk information to health care professionals and the public. Interventions are normally communicated broadly as a mechanism to show accountability.



# Canada Vigilance Program

- Spontaneous Adverse Reaction Reporting Program exists since 1965
- Canada Vigilance Program (name change 2007)
- Mandatory reporting for Market Authorization Holders (i.e. manufacturers)
- Voluntary reporting for Health Professionals and Consumers
- Legislative Framework (e.g. *Food and Drugs Act and Regulations* (C.01.016), Access to Information and Privacy Act etc.)



# Purpose of Adverse Reaction Reporting Program

- Detection, prioritization, confirmation and risk management of signals
- SIGNAL – reported information on a possible causal relationship between an adverse event and a health product the relationship being unknown or incompletely documented previously



# Mandatory Reporting Market Authorization Holders (MAH)

- AR reports submitted by MAHs are collected by the Canada Vigilance National Office located in Ottawa
- MAHs are responsible as per the *Food and Drug Regulations* for the reporting of ARs to Health Canada
- Domestic AR report information is entered into the Canada Vigilance Database



# Adverse Reaction Reports

- Domestic Adverse Reaction Reports
  - Reports concerning reactions occurring in Canada to a product that is marketed in Canada
  - Market Authorization Holder reporting within 15 calendar days of receiving the information (expedited reporting)
  - Serious Adverse Reactions
  - Unusual failure in efficacy reports for new drugs
- Foreign Adverse Reaction Reports
  - Reports concerning reactions occurring outside Canada to a product with the same combination of active ingredients that is marketed in Canada
  - Market Authorization Holder reporting within 15 calendar days of receiving the information (expedited reporting)
  - Serious Unexpected Adverse Reactions



## Canada Vigilance Regional Offices

- Collection of reports, review for completeness, follow-up with reporters
- Initial Data Entry into Canada Vigilance Workflow
- Provide acknowledgement letters to the reporters
- Increase health professional and consumer awareness of Canada Vigilance
- Provide guidance, in order to maximize the quality of reports
- Direct Canadians to Health Canada sources of new safety information
- Consumer Reporting Form/Guidelines Project for reporting of adverse reactions



## Reporting to Canada Vigilance

- Adverse reaction reporting form
  - Available Regional/National Offices, MedEffect website, CPS
- Submit by fax or mail
- On-Line submission
- Toll Free Telephone and Fax
- Verbal reports accepted
- Postage paid mail

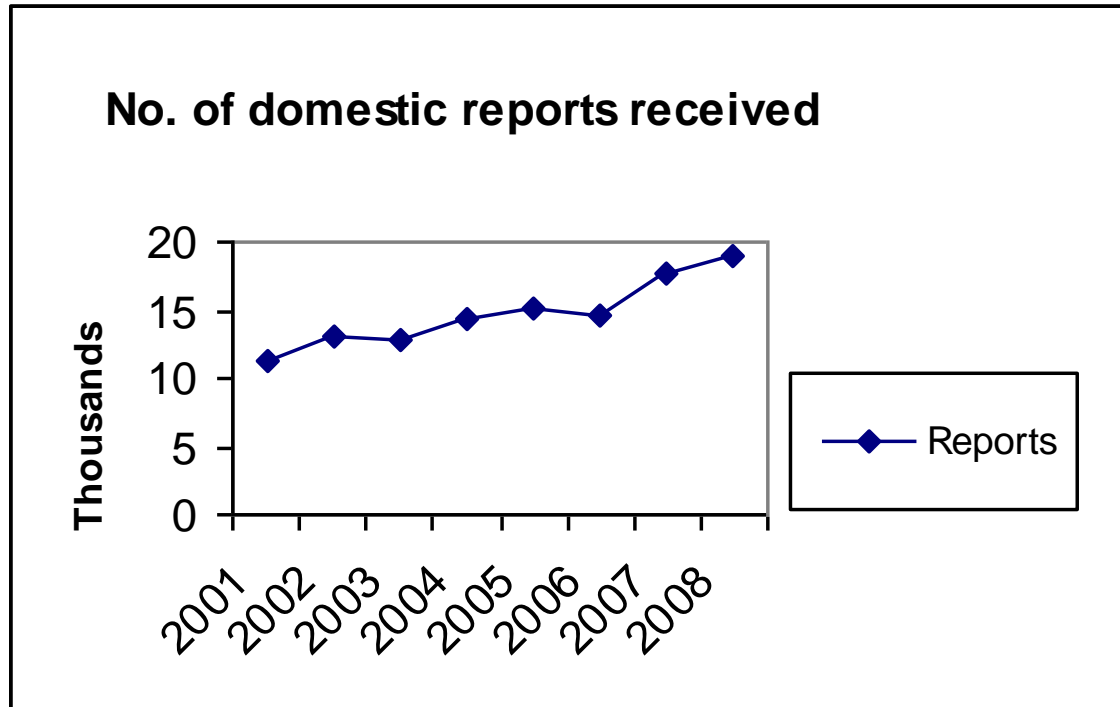


## Scope

- The Canada Vigilance Program collects adverse reaction reports for the following marketed health products approved for use in humans:
  - Pharmaceutical drugs (prescription and non-prescription)
  - Biologics (Schedule D, biotechnology products, therapeutic and diagnostic vaccines and fractionated blood products)
  - Radiopharmaceuticals drugs
  - Natural health products
  - Cells, Tissues and Organs (CTOs)



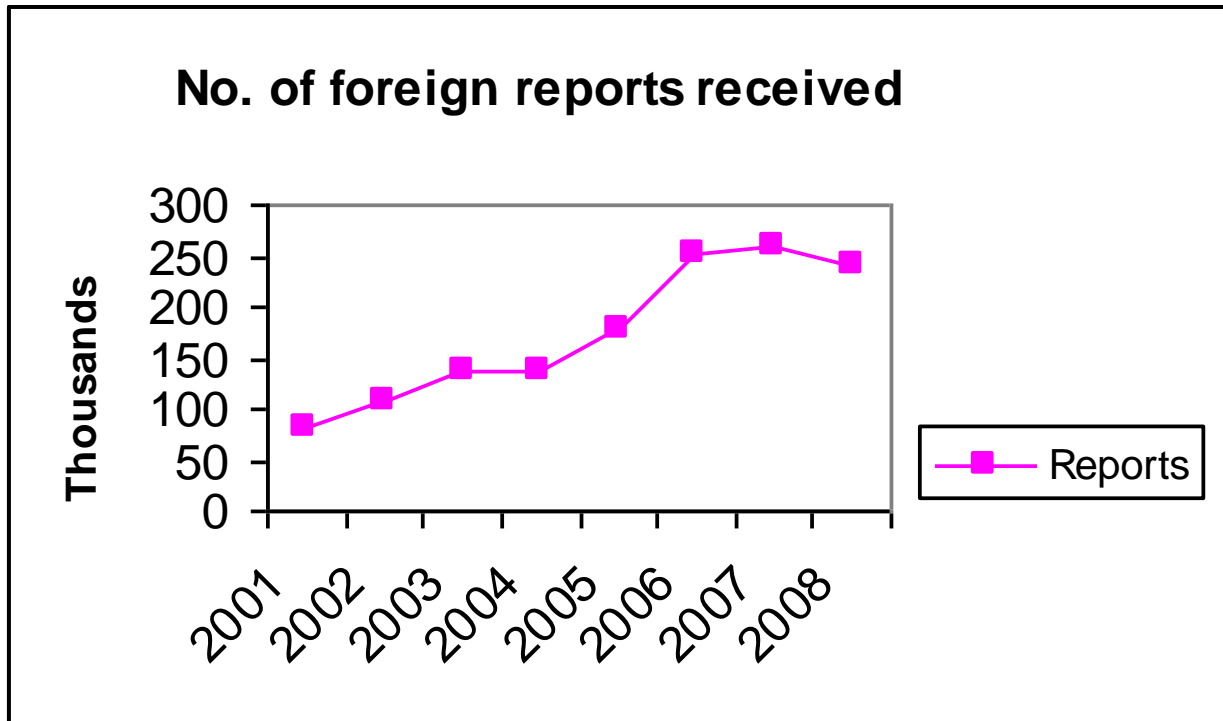
# Canada Vigilance Program Domestic Reports



20,360 Domestic Reports Received in 2008



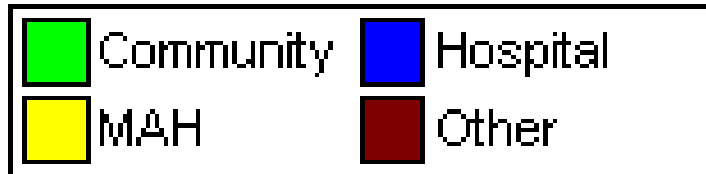
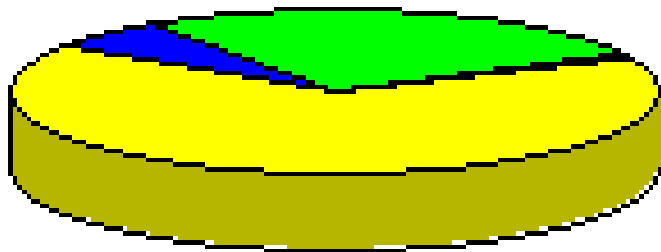
# Canada Vigilance Program Foreign Reports



241,417 Foreign Reports Received in 2008



## Source of Domestic Reports - 2008



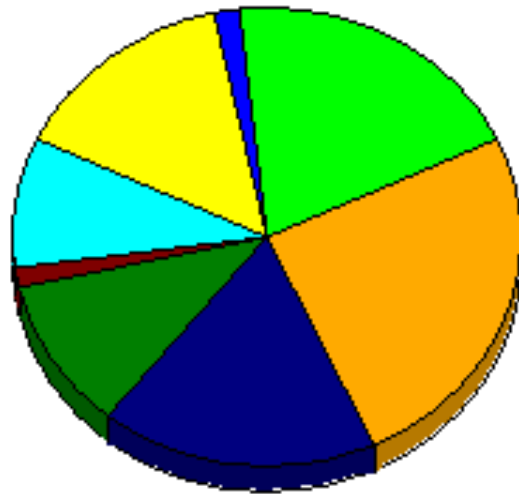
Source	Percentage
Community *	27.57 %
Hospital	6.04 %
MAH **	65.58 %
Other	0.80 %
<b>Total:</b>	<b>100.00%</b>













\* Community – Consumer, patient and non-hospital based health care professionals

\*\* MAH – Market Authorization Holder (MAH)



## Reporter Type – Domestic Reports - 2008



 Consumer	 Coroner/Medical Examiner
 Dentist	 Health Professional
 Lawyer	 Naturopath
 Nurse	 Other
 Patient	 Pharmacist
 Physician	 Physician, specialized

Reporter Type	Percentage
Consumer	19.63 %
Coroner/Medical Examiner	1.54 %
Dentist	0.02 %
Health Professional	14.85 %
Lawyer	0.15 %
Naturopath	0.01 %
Nurse	9.05 %
Other	1.50 %
Patient	10.55 %
Pharmacist	17.81 %
Physician	24.85 %
Physician, specialized	0.04 %
<b>Total:</b>	<b>100.00%</b>



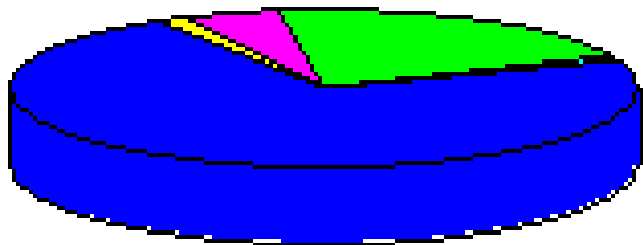
## Serious Domestic Reports - 2008



Serious	Percentage
No	30.75 %
Yes	69.25 %
<b>Total:</b>	<b>100.00%</b>



## Product Type – Domestic Reports - 2008

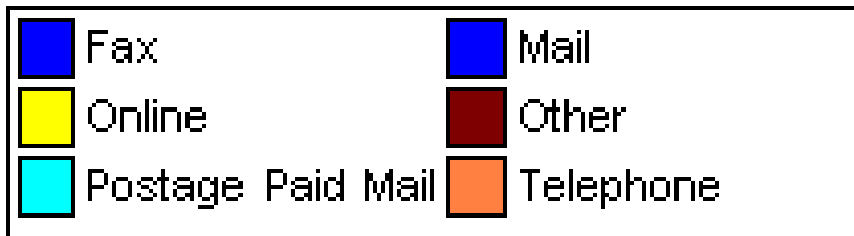
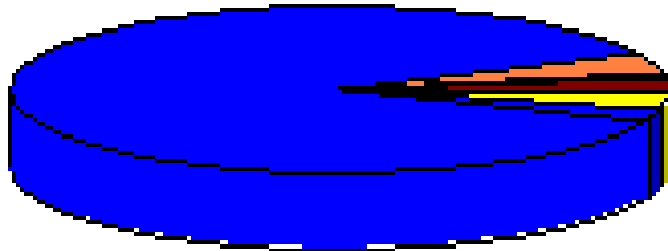


	Biotechnology Products
	Blood Products and Biologics
	Natural Health Products
	Pharmaceuticals
	Radiopharmaceuticals

Product Type	Percentage
Biotechnology Products	20.21 %
Blood Products and Biologics	4.97 %
Natural Health Products	1.72 %
Pharmaceuticals	71.32 %
Radiopharmaceuticals	1.78 %
<b>TOTAL:</b>	<b>100.00%</b>



## Reporting Method – Domestic Reports - 2008



Initial Reporting Method	Percentage
Fax	86.80 %
Mail	1.91 %
Online	3.59 %
Other	2.44 %
Postage Paid Mail	0.30 %
Telephone	4.96 %
<b>Total:</b>	<b>100.00%</b>



## Adverse Reaction Data

- Each report represents the suspicion, opinion or observation of the individual reporter
  - Cause and effect relationships have not been established in the vast majority of reports submitted
  - Only a small proportion of suspected adverse reactions are reported to the program, consequently this information must not be used to estimate the incidence of adverse reactions



# MedEffect™ Canada Initiative

- Launched in August 2005 to better communicate health product safety information and increase awareness of AR reporting
- Centralized access to :
  - Reliable & relevant health product safety information
  - Advisories & CARN
  - Information on how to report ARs & other reporting initiatives
  - Industry Guidance & Templates for Issuance of Health Professional & Public Communications



**MedEffect Canada**  
*Together we can improve health product safety*

**Adverse Reactions to Drugs and Other Health Products**

*Get Informed!  
 Keep Informed!  
 Report Adverse Reactions.*

[www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Advisories, Warnings and Recalls	Guidance Documents
Adverse Reaction Reporting	Adverse Reaction Database
Sign-up for MedEffect e-Notice	



# MedDRA Terminology

## Medical Dictionary for Regulatory Activities

- MedDRA Implemented with Canada Vigilance
- Standardized terminology for classification, retrieval, presentation and communication of medical information (ICH standard)
- Scope: symptoms, signs, diseases and diagnoses, investigations and tests, therapeutic indications, surgical and medical procedures, & medical, social and family history
- Includes medication error related terms
- Sharing of data requires consistency of data coding and assessment
- Facilitates standardized electronic transmission of medical information
- Terminology and MedDRA training provided free of charge to academic researchers



# Canada Vigilance Online Reporting Form

The Canada Vigilance Adverse Reaction (AR) Monitoring Program offers health professionals and the public the ability to complete and submit an AR report online through the MedEffect™ Canada website.

The screenshot shows the top navigation bar with the Health Canada logo and bilingual text. Below it is a menu with links for Français, Contact Us, Help, Search, and Canada Site. A secondary menu includes Just For You, It's Your Health, Media Room, A-Z Index, and Home. The main header features the Health Canada logo and the text 'Drugs & Health Products'. The breadcrumb trail reads: Home > Drugs & Health Products > MedEffect > Adverse Reaction Reporting. The title of the form is 'Canadian Adverse Drug Reaction Monitoring Program Form HC/SC 4016', with a note that it is 'PROTECTED B (when completed)'. The section is identified as 'Section 1 of 5'. Navigation buttons for 'View', 'Reset', 'Guide', and 'Next >' are present. The form content includes a question about follow-up reports, a tracking number field, and five numbered sections for patient information: 1. Identifier (name), 2. Age at time of reaction, 3. Sex (Male/Female), 4. Height (ft/in or cm), and 5. Weight (lbs or kgs). A second set of navigation buttons is located at the bottom of the form area. The footer contains the text 'Last Update: 2006-06-28' and a link to 'Important Notices'.



# Canada Vigilance Online Database

This database is available on the MedEffect™ Canada website and enables users to query AR report-related information extracted from the Canada Vigilance AR database. This site will be undergoing a re-design to improve the search capabilities.

Health Canada Santé Canada

Français Contact us Help Search Canada Site

Drugs & Health Products

Health Canada Home

### CADRMP Online Query

#### 1. Report Search Criteria

Date Received at MHPD:

From Date: 1965 - 01 (YYYY-MM)

To Date: 2008 - 12 (YYYY-MM)

Data will be updated quarterly.

#### 2. Health Product Search Criteria

Health Product Name: [Health Product Name Search \\*](#) - OR - [Active Ingredient Search \\*](#)

Health Product Involvement: Suspected

#### 3. Patient Search Criteria

Age From: 0 Year(s) Old To: ALL Year(s) Old

Gender: ALL

Outcome: ALL

Submit

[Search Assistance Notes](#)  
[Glossary of Database Fields](#)

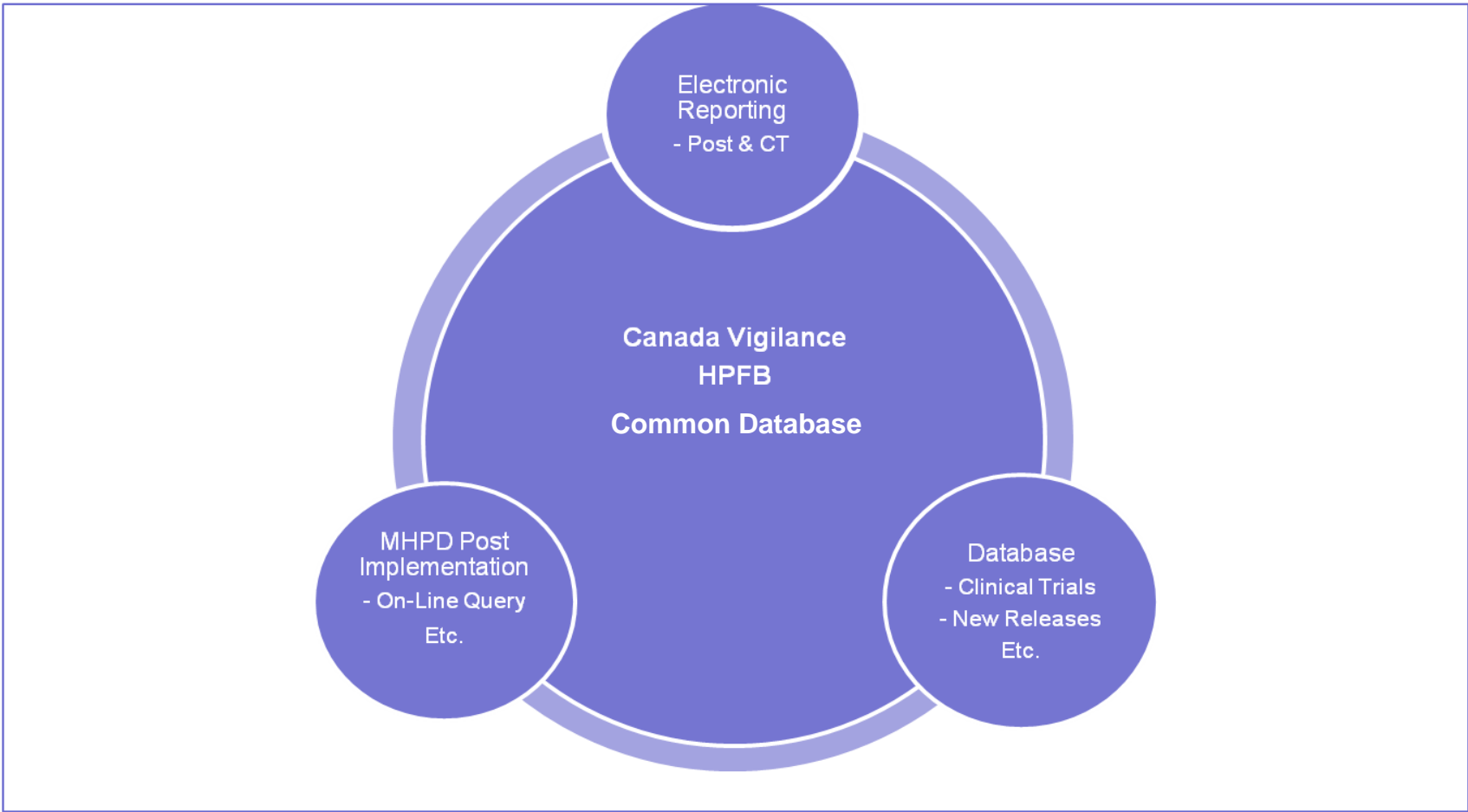
\*Mandatory Search Criteria

Last Updated - 2007-05-15 [Important Notices](#)





# Canada Vigilance Database – Health Products & Food Branch



## Data Management and Standards

- Data Management and Standards are important to Adverse Reaction Reporting and Assessment
- International Sharing of data between Regulatory Agencies requires consistency of data coding and assessment
- ICH (International Conference on Harmonization)
- HL7 (Health Level Seven)
- Other organizations: WHO International Drug Monitoring Program and CIOMS (Council for International Organizations of Medical Sciences)



## Canada Vigilance: Privacy

- Access to Information and Privacy Acts
- Privacy Impact Assessment
- Threat Risk Assessment



# Privacy Principles

- Accountability for Personal Information
- Collection of Personal Information
- Consent
- Use of personal Information
- Disclosure and Disposition of Personal Information



# Privacy Principles

- Accuracy of Personal Information
- Safeguarding Personal Information
- Openness
- Individual's Access to Personal Information
- Challenging Compliance



## Registries

- Tool used in surveillance of patients and products
- Require development in accordance with privacy act
- Established by a variety of organizations (Manufacturers, CIHI)
- Examples of registries: Clozapine (manufacturer), Hip Implants (CIHI)
- Health Canada does not establish or fund registries
- Progressive Licensing Project will include regulatory requirements for post-market commitments depending on the information available in the pre-market phase which could include a registry





Health  
Canada Santé  
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Your health and  
safety... our priority.

Votre santé et votre  
sécurité... notre priorité.



# Canada Vigilance

Adverse Reaction Monitoring Program and Database

Suspect an adverse reaction?  
**Report it...**

**Phone:** 1-866-234-2345

**Fax:** 1-866-678-6789

**Online:** [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

**Postage Paid Mail**

A Program of  
MedEffect Canada  
*Together we can improve health product safety*

Canada

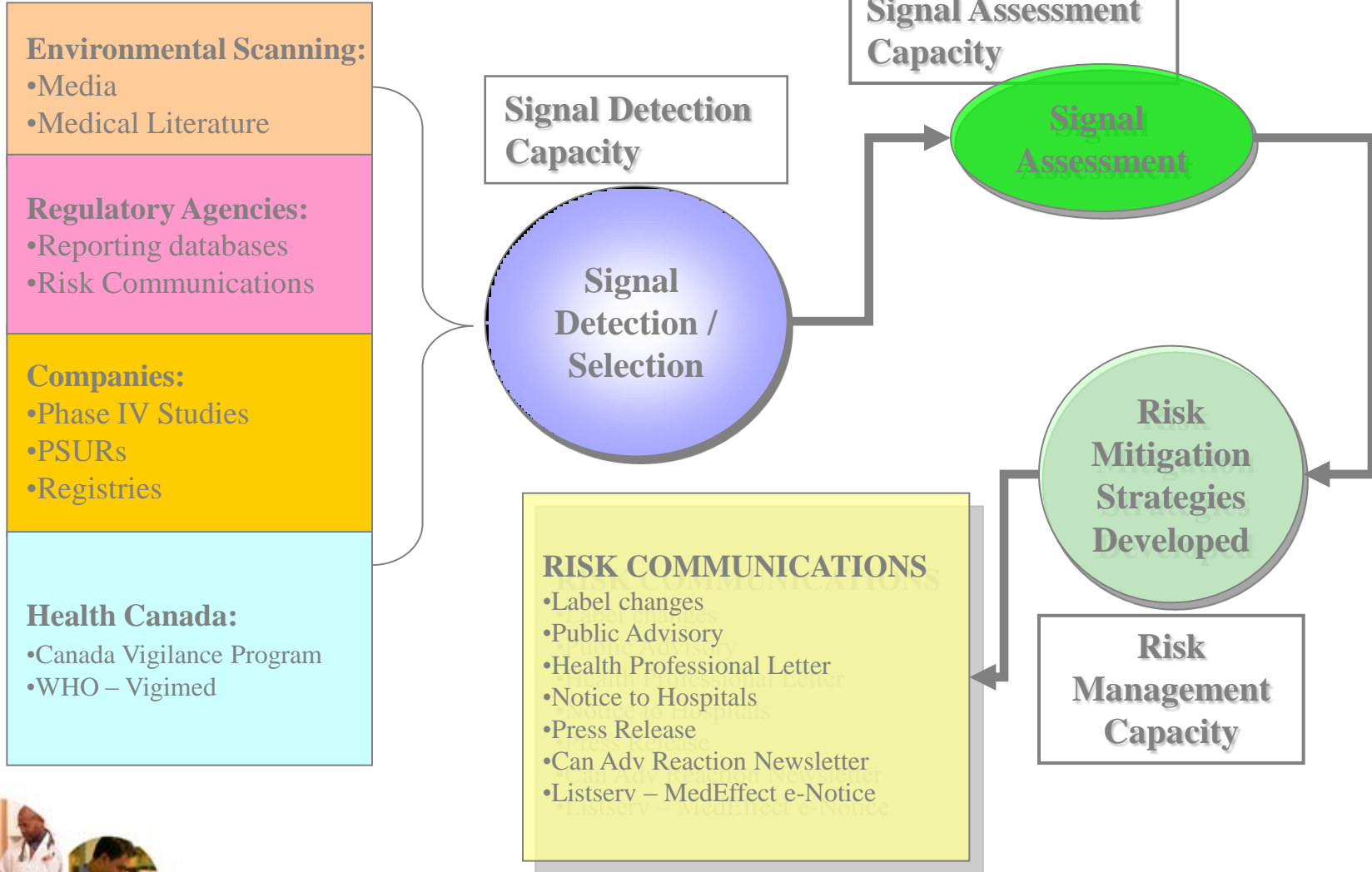


# Background Information



# Integrating Multiple Sources

Monitoring Inputs



# Canada Vigilance Database: Business Requirements

- Clinical trial AR requirements
- Post market AR requirements
- Signal Detection & powerful query tools
- ICH compliant (E2B, MedDRA, ESTRI-Gateway)
- Management & ICSR reporting
- Scanning and Imaging
- Capability for future integration document management solution, small manufacturer reporting interface



## Canada Vigilance Database

- The Canada Vigilance database is comprised of an integrated and complementary suite of 3 applications which include:
  - Core application
  - Signal detection tool
  - ESTRI gateway module



## Canada Vigilance Database: Core Application

- For the collection, coding, assessment and reporting of adverse reaction data
- Workflow module routes AR cases to Specialists/Assessors automatically, based on pre-defined criteria such as drug class, seriousness, etc.
- Enables full compliance with the ICH international AR reporting requirements, such as ICH E2B, MedDRA coding, etc.
- Configurable and will offer English and French user interfaces
- Scanned images of AR reports



## Canada Vigilance Database: Signal Detection

- Data mining and signal detection tool
- Facilitates safety data analysis
- Facilitates the identification of patterns in the data and identify possible associations underlying signals
- Users can build, save and share ad-hoc queries
- Provides access to the FDA (FOI) data, a larger pool of data for analysis and signal detection
- Statistical module includes algorithmic analyses, such as PRR, Bayesian, Chi-Square, Log-Likelihood



# Signal Detection: Standard Reports

The screenshot displays the SafetyMart web application interface. At the top, the browser title is "SafetyMart - Microsoft Internet Explorer". The application header includes the SafetyMart logo and navigation tabs for "Analysis Modules", "Reports", and "Admin". Below the header, the "Universe" is set to "SafeMart" and a "Report Designer" button is visible. The main content area is divided into two panels: "Report Groups" on the left and "Report Names" on the right. The "Report Groups" panel lists: 1. StandardReports, 2. EUCTD, 2. Line Listing, and 3. SMQS. The "Report Names" panel lists several reports, each with a folder icon: Adverse Event Count Per Month, Adverse Event Count Per Year, Dechallenge Rechallenge Case Count, Number of Serious Adverse Events and Cumulative Total Over Time, Number of Serious and Non-Serious Cases by SOC Level, Serious Adverse Events - Labeled vs Outcomes by Drug, Serious Adverse Events by Age Grouping and Gender by Drug, Serious Count Per Month, and Serious Count Per Year. A mouse cursor is positioned over the bottom of the "Report Names" panel.





# Signal Detection: Statistical Analysis

Statistical Analysis Output - Microsoft Internet Explorer

**SafetyMart**

Analysis Modules   Reports   Admin

Statistical Analysis Output

SafetyMart

Back Home Selection Criteria Save

Refresh Print Preview Export to Excel Statistical Analysis Tool

Reaction Level  Refresh Include All Clear Clear All

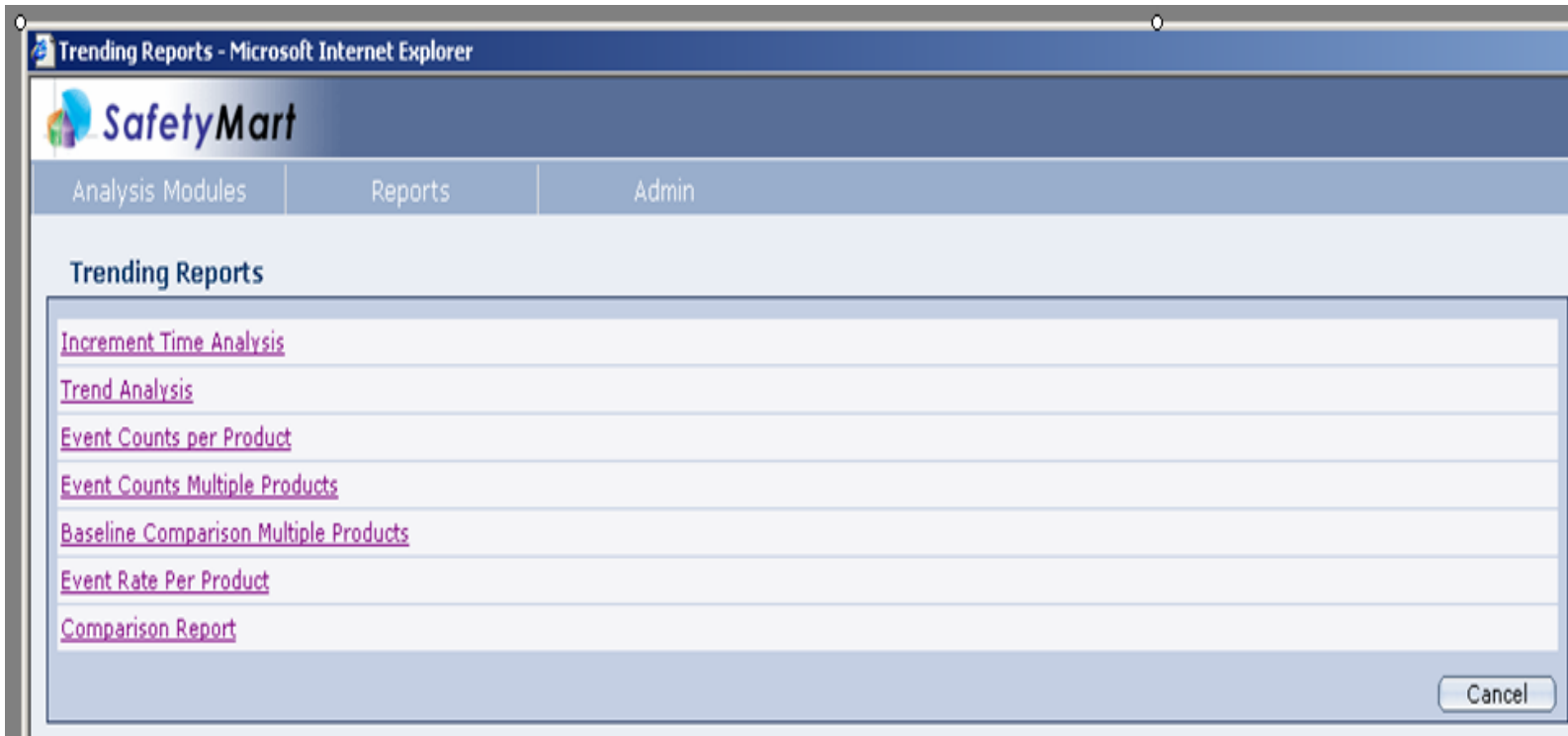
Graphical View Drilldown Hierarchy

Select	Drug	Reaction	N	PRR	ROR	EB05	EBGM	X <sup>2</sup>	X <sup>2</sup> is significant at a significance level of <= @	LogLikelihood Ratio (G)	G is significant at a significance level of <= @	BCPNN
<input type="checkbox"/>	CHAMPIX	SUICIDAL IDEATION	43	30.21	35.329	4.477	30.802	1220.71 <sup>a,b</sup>	0.001	212.81 <sup>a</sup>	0.001	4.917

a - Yates correction for continuity used. (Yates, 1934)  
 b - The contingency table for X<sup>2</sup> analysis has expected values greater than the absolute difference between observed and expected values  
 Log-likelihood ratio analysis (G) should be used. (Williams, 1976)  
 @ - If blank, the significance is greater than 0.100



# Signal Detection: Trend Analysis



The screenshot shows a web browser window titled "Trending Reports - Microsoft Internet Explorer". The page header features the "SafetyMart" logo and a navigation menu with three items: "Analysis Modules", "Reports", and "Admin". The "Reports" menu is active, displaying a list of report options under the heading "Trending Reports". The options are: [Increment Time Analysis](#), [Trend Analysis](#), [Event Counts per Product](#), [Event Counts Multiple Products](#), [Baseline Comparison Multiple Products](#), [Event Rate Per Product](#), and [Comparison Report](#). A "Cancel" button is located in the bottom right corner of the report list area.



# Canada Vigilance Database: Trend Analysis Outputs

**SafetyMart**

Analysis Modules | Reports | Admin

**Output**

SafetyMart

◀ Back | 📄 Selection Criteria | 🖨️ Print Preview | 📄 Export to Excel

**PRR Code**

	>10
	>5 to <=10
	>3 to <=5
	<=3

Drug : CHAMPIX << ≤ 16 17 18 19 20 ≥ >>

Event	Q1, 2007	Q1, 2007 - Q2, 2007	Q1, 2007 - Q3, 2007	Q1, 2007 - Q4, 2007
Suicidal ideation	0	0	5	10
Syncope	0	0	1	1
Syncope vasovagal	0	0	0	1
Tachycardia	0	0	0	1
Thinking abnormal	0	0	0	2
Throat tightness	0	0	1	2
Thrombophlebitis superficial	0	0	0	1
Tinnitus	0	0	0	1
Tremor	0	0	1	3
Urinary incontinence	0	1	1	2



# Canada Vigilance Database: Electronic Exchange

- ESTRI Gateway module
- Enables the secure electronic exchange and management of safety information in the ICH E2B and M2 standards
- Planned implementation for Phase 2 of this project

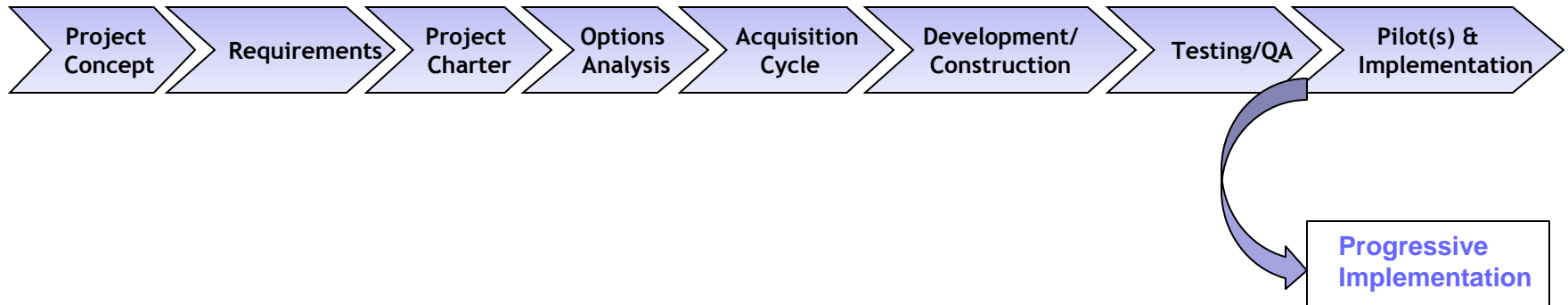


## Canada Vigilance Database Sub-Projects

- Post-Market Implementation (MHPD)
- Sustainability and On-Going Maintenance
- Post-Market On-Line Database
- Clinical Trials Implementation (BGTD, NHPD, TPD)
- Electronic Reporting by Small/Medium/Large MAH/Sponsors
- Signal detection business transformation project underway



# Electronic Reporting by Small/Medium/Large MAHs/Sponsors



## Proposed Timeline

- Acquisition Cycle Fall 2009
- Electronic Reporting Pilots starting Fall 2010
- Staggered implementation by small/medium/large MAHs



# Questions?

