Canada Vigilance
Adverse Reaction Monitoring Program and Database

Network of Rare Blood Disorder Organizations
Friday November 13, 2009

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Marketed Health Products Directorate
Health Canada
Objective

• MedEffect™ Canada/Canada Vigilance Program and Database

• Data Management and Standards

• Privacy
Post-market surveillance is composed of three major activities:

1. **Information collection, processing and assessment**
   - 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.

2. **Signal Detection and Evaluation**
   - 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.

3. **Risk management (interventions)**
   - 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

No. of domestic reports received

Thousands

2001 2002 2003 2004 2005 2006 2007 2008

20,360 Domestic Reports Received in 2008
Canada Vigilance Program Foreign Reports

241,417 Foreign Reports Received in 2008
Source of Domestic Reports - 2008

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community*</td>
<td>27.57 %</td>
</tr>
<tr>
<td>Hospital</td>
<td>6.04 %</td>
</tr>
<tr>
<td>MAH **</td>
<td>65.58 %</td>
</tr>
<tr>
<td>Other</td>
<td>0.80 %</td>
</tr>
<tr>
<td><strong>Total</strong>:</td>
<td><strong>100.00%</strong></td>
</tr>
</tbody>
</table>

* Community – Consumer, patient and non-hospital based health care professionals
** MAH – Market Authorization Holder (MAH)
Report Type – Domestic Reports - 2008

<table>
<thead>
<tr>
<th>Reporter Type</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Consumer</td>
<td>19.63 %</td>
</tr>
<tr>
<td>Coroner/Medical Examiner</td>
<td>1.54 %</td>
</tr>
<tr>
<td>Dentist</td>
<td>0.02 %</td>
</tr>
<tr>
<td>Health Professional</td>
<td>14.85 %</td>
</tr>
<tr>
<td>Lawyer</td>
<td>0.15 %</td>
</tr>
<tr>
<td>Naturopath</td>
<td>0.01 %</td>
</tr>
<tr>
<td>Nurse</td>
<td>9.05 %</td>
</tr>
<tr>
<td>Other</td>
<td>1.50 %</td>
</tr>
<tr>
<td>Patient</td>
<td>10.55 %</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>17.81 %</td>
</tr>
<tr>
<td>Physician</td>
<td>24.85 %</td>
</tr>
<tr>
<td>Physician, specialized</td>
<td>0.04 %</td>
</tr>
</tbody>
</table>

Total: 100.00%
Serious Domestic Reports - 2008

<table>
<thead>
<tr>
<th>Serious</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>No</td>
<td>30.75 %</td>
</tr>
<tr>
<td>Yes</td>
<td>69.25 %</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>100.00%</strong></td>
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</tbody>
</table>
Product Type – Domestic Reports - 2008

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotechnology Products</td>
<td>20.21 %</td>
</tr>
<tr>
<td>Blood Products and Biologics</td>
<td>4.97 %</td>
</tr>
<tr>
<td>Natural Health Products</td>
<td>1.72 %</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>71.32 %</td>
</tr>
<tr>
<td>Radiopharmaceuticals</td>
<td>1.78 %</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>100.00%</strong></td>
</tr>
</tbody>
</table>
Reporting Method – Domestic Reports - 2008

- Fax: 86.80%
- Mail: 1.91%
- Online: 3.59%
- Other: 2.44%
- Postage Paid Mail: 0.30%
- Telephone: 4.96%

Total: 100.00%
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
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
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.
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.
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
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
Postage Paid Mail
Background Information
Integrating Multiple Sources

**Environmental Scanning:**
- Media
- Medical Literature

**Regulatory Agencies:**
- Reporting databases
- Risk Communications

**Companies:**
- Phase IV Studies
- PSURs
- Registries

**Health Canada:**
- Canada Vigilance Program
- WHO – Vigimed

**Signal Detection/Capacity**

**Signal Assessment/Capacity**

**Risk Mitigation Strategies Developed**

**Risk Management Capacity**

**RISK COMMUNICATIONS**
- Label changes
- Public Advisory
- Health Professional Letter
- Notice to Hospitals
- Press Release
- Can Adv Reaction Newsletter
- Listserv – MedEffect e-Notice

**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
Signal Detection: Analysis Tool

![Analysis Tool Interface](image_url)
Signal Detection: Statistical Analysis

![Statistical Analysis Output](image-url)

- **Select**
  - Drug
  - Reaction
  - \( N \), \( PRR \), \( ROR \), \( EB05 \), \( EBGM \)

- **Statistical Analysis Output**
  - \( \chi^2 \)
  - LogLikelihood Ratio (G)
  - G is significant at a significance level of \( \leq 0.05 \)

- **Graphical View**

- **Drilldown Hierarchy**

- **Analysis Modules**
  - Reports
  - Admin

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a - Yates correction for continuity used. (Yates, 1934)
b - The contingency table for \( \chi^2 \) 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

- Increment Time Analysis
- Trend Analysis
- Event Counts per Product
- Event Counts Multiple Products
- Baseline Comparison Multiple Products
- Event Rate Per Product
- Comparison Report
## Canada Vigilance Database: Trend Analysis Outputs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Syncope vasovagal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thinking abnormal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Throat tightness</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thrombophlebitis superficial</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
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?