MedDRA, an ICH Product
A Regulator’s Experience
Part Two – Health Canada Experience
Health Canada and MedDRA

- Established international medical terminology that is used throughout the regulatory process
  - **Clinical trials**
    - Medical history, adverse events
  - **Labelling**
    - Product Monograph
  - **Post-Market Surveillance**
    - Suspect Adverse Reactions (medical history, reactions, investigations, indications)
  - **Safety studies**
    - Facilitates consistency of data coding, data assessment and data analysis
    - Facilitates standardized electronic transmission of medical information
MedDRA - Canada Vigilance Database

- New pharmacovigilance information system implemented within Health Canada’s post market surveillance environment, March 2008
- Enables compliance with the ICH international Adverse Reaction (AR) reporting requirements, including MedDRA
MedDRA – Canada Vigilance Sub-Projects

- Post-Market implementation – 2008
- Pre-Market implementation (Clinical Trials) – 2011
- Post-Market On-Line Database
- Electronic Reporting by Small/Medium/Large MAH/Clinical Trial Sponsor
- Signal Detection and Data Mining
Canada Vigilance Database

• Supports MedDRA coding for the following terms:
  o Reaction terms
  o Patient history
  o Indications
  o Laboratory tests
• Stores Reported Term, Primary SOC, PT and LLT (coding level)
• Includes both French and English user interfaces
Implementation of MedDRA

- Legacy Database Conversion:
  - Canadian Adverse Drug Reaction Information System (CADRIS)
  - Contained suspected Adverse Reaction (AR) reports for Canadian marketed health products reported to Health Canada since 1965
  - Reaction terms coded in WHO-ART terminology
Terminology Conversion Strategy

- Legacy data conversion:
  - WHO-ART terminology was included in the development of MedDRA
    - Every WHO-ART term has a corresponding term in the MedDRA terminology
    - Not necessarily at the same level of the hierarchy
  - WHO Uppsala Monitoring Centre (UMC) has developed with ICH/MSSO a “bridge” or mapping from WHO-ART to MedDRA:
    - Allows conversion of legacy data from WHO-ART to MedDRA
    - Maintained current with every version release of WHO-ART and MedDRA
    - Does not work in the other direction since MedDRA is more granular than WHO-ART
Terminology Conversion Strategy

1. Data review:
   • Outliers were identified, documented and corrected prior to data conversion and migration

2. Mapping exercise:
   • Developed conversion table of WHO-ART term to equivalent MedDRA v11.0 (current/non-current) term, (vendor mapping process) e.g.:

<table>
<thead>
<tr>
<th>Whoart Lx Id</th>
<th>Reaction Term</th>
<th>MedDRA Reaction Term version 11.0</th>
<th>MedDRA LLT Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>101002100210</td>
<td>hypertension</td>
<td>Hypertension</td>
<td>10020772</td>
</tr>
</tbody>
</table>

3. Data conversion and migration:
   • Performed by vendor

4. Testing, Quality Control and Validation
MedDRA Training

Health Canada:
• 4 training sessions, 3 modules offered at implementation, Biannual – ongoing:
  o Introductory Webinar
  o Hands-on Coding with MedDRA
  o Hands-on Safety Data Analysis and Standardized MedDRA Queries (SMQ’s)

Industry:
• Collaborated with the MSSO to offer MedDRA training to subscribers, 2 modules offered
Implementation of MedDRA

**Documentation**

- Guidance Document for Industry: Reporting Adverse Reactions to Marketed Health Products
- Organization specific MedDRA Coding Conventions based on the MedDRA Term Selection: Points to Consider document (ICH endorsed guide for MedDRA users)
  - Updated biannually with each MedDRA version release
Documentation

- Updated MedDRA fact sheet on the Health Canada website
- Quality Assurance Procedures for monitoring MedDRA coded data
- Versioning Strategy Procedure
- Submitting a Change Request to the MSSO
- Use of MedDRA terms and Standardized MedDRA Queries (SMQ’s) for signal detection
Quality Assurance

- Monitor quality of MedDRA coded data
- Verify adherence to and deviation from MedDRA Coding Conventions SOP
- Compare verbatim (Reported Term) versus coded MedDRA LLT term
**Departmental MedDRA Working Group**

- Forum for discussion with respect to the implementation and use of MedDRA within the Department
- Ensure coordination and harmonization of the use of MedDRA terminology
- Serve as the channel to review and process MedDRA Change Requests
- Educate, promote and disseminate MedDRA information both within the department and externally e.g. academia, industry
Post MedDRA Implementation

Versioning

• Follow MSSO’s recommendations for semi-annual version control
  o Re-code historical data (automatic and minimal manual)
  o Synchronize with ICH regions (first Monday of the second month after its release, midnight GMT, Sunday to Monday)
  o Example – MedDRA 14.1 released 1st September and synchronized 7th November

• Versioning allows Health Canada to profit from the continual enhancements that are ongoing with the MedDRA terminology
MedDRA in Pharmacovigilance

Health Canada – MedDRA in Pharmacovigilance

• **MedDRA** (Medical Dictionary for Regulatory Activities) is an internationally accepted, clinically validated medical terminology used to facilitate the regulation of medical products. This standardized dictionary of medical terms is used throughout the regulatory process to enter, retrieve, analyse and present data both before and after a product has been authorized for sale.
Health Canada’s Pharmacovigilance Process Overview

**Sources**

### Scanning:
- Media
- Medical and scientific literature

### International Regulatory Agencies:
- Databases
- Warnings/Advisories

### Manufacturer:
- Phase IV studies
- PSURs
- Registries

### Health Canada:
- CanadaVigilance
- WHO – Vigimed
- Pre-market Safety Info.

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**Signal**

**Identification**

**Risk management**

**Signal Detection**

**Prioritization**

**Risk Management Strategy**

**Evaluation**

**Risk Communication**

- Market withdrawal, labelling change, recall

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**Signal evaluation**

- Public Advisory
- Health Professional Communication
- Notice to Hospitals
- Media
- Cdn Adverse Reaction Newsletter
- MedEffect/MedEffet
- It's Your Health

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**MedDRA in Pharmacovigilance**
Canada Vigilance – Data Management/Assessment

• MedDRA terminology is a foundation for pharmacovigilance activities
  o Adverse reactions
  o Patient’s medical history
  o Indication for the suspected product(s)
  o Laboratory tests (as adverse reaction terms)

• Data coded using MedDRA LLTs (Lower Level Terms)

• Reference
  o Points to Consider Document - MedDRA Terms Selection
Impact of MedDRA on Canada Vigilance data management

- Increased size/granularity has resulted in better (i.e., more accurate) representation of data.
- Primary and secondary SOC allocations allow for different “views” of the data.
- Lower level terms have allowed more precise matching with reporter information.
- Terms are up to date and medically verified as a result of maintenance processes.
Canada Vigilance – Data Retrieval

- Knowledge of structure and characteristics of MedDRA and data allows flexibility according to needs
- Search: how inclusive or exclusive should it be?
  - Combination of MedDRA PT, HLT, HLGT and SOC Levels
  - SMQs
  - Customized retrieval strategy
- Reference
  - Points to Consider Document - Data Retrieval and Presentation

Crucial: quality of submitted reports, quality of MedDRA coding
Canada Vigilance – Data Retrieval

Standardized MedDRA Queries (SMQs)

• Used in Clinical and post-market setting by regulatory agencies and pharmaceutical companies

• SMQs: global consistency in retrieving MedDRA adverse reaction data for analysis of specific medical concepts over time and multiple organizations

• Included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to medical condition or area of interest.
SMQs in Production - Examples

- As of version 14.0, a total of 84 in production (Other SMQs in development)
  - Adverse pregnancy outcome/reproductive toxicity (includes neonatal disorders)
  - Agranulocytosis
  - Anaphylactic reaction
  - Cerebrovascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Ischaemic heart disease
  - Lack of efficacy/effect
  - Peripheral neuropathy
  - Pseudomembranous colitis
  - Rhabdomyolysis/myopathy
  - Severe cutaneous adverse reactions
  - Reactions
  - Systemic lupus erythemtosus
Narrow and Broad Searches

- “Narrow” scope – specificity (cases highly likely to be condition of interest)
- “Broad” scope – sensitivity (all possible cases)
- “Broad search” – all broad + all narrow terms
- MedDRA term can be broad or narrow depending on SMQ
  - Example: PT Renal failure acute
    - Narrow in Acute renal failure (SMQ)
    - Broad in Rhabdomyolysis/myopathy (SMQ)
**SMQ Applications**

- **Clinical Trials**
  - Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
  - Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)

- **Post-marketing**
  - Selected SMQs to retrieve cases for suspected or known safety issue
  - Signal detection (multiple SMQs employed)
  - Single case alerts
  - Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)
Canada Vigilance – SMQs

• Proven as an effective method for retrieving data and scanning the Canada Vigilance Database

• Examples of commonly used SMQs:
  o Hepatic disorders SMQ
  o Torsade de pointes / QT prolongation SMQ
  o Severe cutaneous adverse reactions SMQ
  o Cardiac arrhythmias SMQ
Canada Vigilance – Potential Signal Identification

Involves multiple sources and complementary processes
- review/monitor domestic Canadian AR data in Canada Vigilance database
- Scanning of Scientific literature
- Monitoring information from other Regulatory Agencies
- Monitor/review safety information submitted by MAHs

Standardized data coded in MedDRA from various sources facilitates data analysis
MedDRA in Pharmacovigilance

Canada Vigilance - Signal Detection Databases

Adverse reaction reports
Workflow system
MedDRA Coded

Extract of all AR reports weekly

Enhance Monitoring
Targeted Monitoring Strategies

Analytical tool

Incorporate Analytical Tools
Data-mining (in development)
Signal Detection Process – CIOMS Working Group VIII
Practical Aspects of Signal Detection in Pharmacovigilance

• **CIOMS** – Council for International Organizations of Medical Sciences

• **Report of CIOMS Working Group VIII** – published 2010

• **Pharmacovigilance** is an evolving discipline though its goals – to detect, assess, understand and prevent drug-related adverse effects – remain constant.

• **Signal Detection – Traditional methods:** case and case series review, focus on Designated Medical Events and Targeted Medical Events, Special Populations, clinical triage of cases for prioritization, estimate of reporting rates, review of aggregate data (eg. PSURs), other sources of data, etc.

• **Signal Detection – Quantitative methods:** simple quantitative filters to complement traditional methods of signal detection, data-mining for systematic statistical disproportionality analyses of large databases – Statistic of Disproportionate Reporting (SDR), triage of outputs, other sources of data, etc.

• **Signal Management:** signal prioritization and signal evaluation including risk management and communication.
Canada Vigilance – Principles for Signal Detection

- Develop a framework to enable monitoring adverse reaction data in a comprehensive and sustainable manner
- Develop processes comparable to international partners
- Assessment of individual case reports and case series
- Targeting monitoring strategies in development
- Statistical analysis a complementary source of information
- Standardized MedDRA coded data is foundation to signal detection processes
Canada Vigilance – Signal Detection

- Methods for signal detection include:
  - Case and case series review
  - Targeted monitoring strategies
  - Quantitative statistical analysis
Signal Detection Process - Case Review Evaluation

- **Case Definition:** a set of MedDRA terms consistent with the adverse event/disorder under evaluation
- Retrieval of data based on case definition for case of interest
- **Case Series:** a case series refers to a collection of adverse reaction reports of patient experiencing similar adverse reaction suspected with the same health product
• Involves monitoring of specific health product and targeted medical event

• **Targeted Medical Events** represent a medical concept described by a predefined set of MedDRA reaction terms that correspond to important identified or potential risks with a health product which require further characterization or evaluation.
Targeted Monitoring - Designated Medical Events

- **Designated Medical Events** are adverse reactions that are considered rare, serious and associated with a high drug-attributable risk and constitute an alarm with as few as 1 to 3 reports (eg. Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, anaphylaxis, aplastic anaemia and torsade de pointes).
Targeted Monitoring - Designated Medical Events

- Database scan for important reactions based on Standardized MedDRA Queries (SMQs) or groups of MedDRA terms.

- For Example:

  Acute pancreatitis
  Agranulocytosis
  Convulsions
  Haematopoietic cytopenias
  Rhabdomyolysis/myopathy
  Torsades de pointes/QT prolongation
  Infections – specific
  Posterior Reversible Encephalopathy Syndrome

  Acute renal failure
  Anaphylactic reaction
  Haemolytic disorders
  Hepatic disorders
  Severe cutaneous adverse reactions
  Guillain-Barré syndrome
Signal Detection – Canada Vigilance

Other Targeted Monitoring Strategies using MedDRA Coded Data

- New active substances
- Special patient populations (e.g. Pediatric, Elderly)
- Specific adverse reaction report outcomes (e.g. Fatal, Hospitalisation)
# Canada Vigilance Database Statistical Analysis

**Example:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Event</th>
<th>N</th>
<th>PRR</th>
<th>PRR025</th>
<th>PRR975</th>
<th>ROR</th>
<th>ROR025</th>
<th>ROR975</th>
<th>ChiSquare</th>
<th>BPCNN</th>
<th>BCPNN025</th>
<th>BCPNN975</th>
</tr>
</thead>
</table>

*dabigatran etexilate – cerebrovascular accident – Last Migration Date: 2011-10-01

The statistical analysis relies on MedDRA terminology

**PRR**  – proportional reporting ratio  
**ROR**  – reporting odds ratio  
**BCPNN**  – Bayesian Confidence Propagation Neural Network
Development for Scanning Canada Vigilance Database for Statistical Significant Trends

- Currently WHO information Component (Bayesian Confidence Propagation Neutral Network) IC values used in signal case work ups.

- Methodology in development for scanning Canada Vigilance database for statistical significant trends.

   To include steps for:
   - Scanning/thresholds
   - Screening/triage
   - Prioritization
   - Analysis
   - Documentation

- Consideration of statistical analysis incorporates the different levels of MedDRA terminology

MedDRA in Pharmacovigilance
Health Canada Experience with MedDRA

- Complete terminology allows data analysis and documentation across the product life cycle
- Diversity of coding provides more specificity with respect to data
- Data coded in MedDRA provides Health Canada with consistent data analysis within the Pharmacovigilance process
Health Canada Experience with MedDRA

- Tools for data review and analysis has enhanced signal detection and data management

- Standardized MedDRA coding and data management is essential for optimal data retrieval and signal detection

- Use of Standardized MedDRA Queries (SMQs) and/or groups of MedDRA terms provides an effective method for scanning the Canada Vigilance Database.
Questions
Background
Canada Vigilance Statistics

Canada Vigilance Program Domestic Reports

32,921 Domestic Reports Received in 2010
Canada Vigilance Statistics

Canada Vigilance Program Foreign Reports

363,961 Foreign Reports Received in 2010
Canada Vigilance Statistics

Canada Vigilance Program Domestic Reports by Product Type

<table>
<thead>
<tr>
<th>Product type</th>
<th>No. (%) of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceuticals</td>
<td>22 104 (67.14)</td>
</tr>
<tr>
<td>Biotechnology products</td>
<td>8 860 (26.91)</td>
</tr>
<tr>
<td>Blood products and biologics</td>
<td>903 (2.74)</td>
</tr>
<tr>
<td>Natural health products</td>
<td>677 (2.06)</td>
</tr>
<tr>
<td>Radiopharmaceuticals</td>
<td>348 (1.06)</td>
</tr>
<tr>
<td>Cells, tissues and organs</td>
<td>29 (0.09)</td>
</tr>
<tr>
<td>Total</td>
<td>32 921 (100.0)</td>
</tr>
</tbody>
</table>

* Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.
## Canada Vigilance Statistics

### Canada Vigilance Program Domestic Reports by Source

<table>
<thead>
<tr>
<th>Source</th>
<th>No. (%) of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAH</td>
<td>25 967 (78.88)</td>
</tr>
<tr>
<td>Community**</td>
<td>5 727 (17.40)</td>
</tr>
<tr>
<td>Hospital</td>
<td>1 120 (3.40)</td>
</tr>
<tr>
<td>Other</td>
<td>107 (0.33)</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>32 921 (100.0)</td>
</tr>
</tbody>
</table>

Note: MAH = Market Authorization Holder.

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

**Consumer, patient and non-hospital based health care professionals.
## Canada Vigilance Statistics

### Canada Vigilance Program Domestic Reports by Originating Reporter

<table>
<thead>
<tr>
<th>Reporter type</th>
<th>No. (%) of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>8 102 (24.61)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>4 615 (14.02)</td>
</tr>
<tr>
<td>Health professional**</td>
<td>5 782 (17.56)</td>
</tr>
<tr>
<td>Nurse</td>
<td>5 100 (15.49)</td>
</tr>
<tr>
<td>Consumer/Patient</td>
<td>8 733 (26.53)</td>
</tr>
<tr>
<td>Dentist</td>
<td>12 (0.04)</td>
</tr>
<tr>
<td>Naturopath</td>
<td>5 (0.02)</td>
</tr>
<tr>
<td>Other</td>
<td>572 (1.74)</td>
</tr>
<tr>
<td>Total:</td>
<td>32 921 (100.0)</td>
</tr>
</tbody>
</table>

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

** Type not specified in report.