

 Health Canada Santé Canada

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# Pharmacovigilance *Challenges*



MedEffect Canada  
Together we can improve health product safety

MedEffet Canada  
Ensemble nous pouvons améliorer l'innocuité des produits de santé

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## Provide Overview of some of the Challenges of Pharmacovigilance *Canadian Perspective*

- History
- Global Perspective
- Canadian Approach
- Challenges



3

### History and Evolution

## Definition

- From the Greek word 'Pharmacon': *DRUG*
- Latin 'Viigilare': *TO KEEP WATCH, AWAKE OR ALERT*
- **SYSTEM** for tracking the safety of products
- Consists of:
  - Regular and timely review,
  - Appraisal and
  - Communication of safety information critical to risk management of products



4

## Key historical events that stimulated regulations

- First UK law to seek to regulate drugs was the 1868 Pharmacy Act
- USA: 1902 Biologics Control Act
- USA: the 1938 Federal Food, Drug and Cosmetic Act was passed, which required proof of safety before the release of a new drug. The category of 'Prescription-Only' drugs was codified into law by 1951.
- The thalidomide tragedy in the early 1960 heralded the modern regulatory system in most western countries.



5

## Safety Elements

- Increasing importance globally
- Safety related activities
  - Regulatory authority has been more limited and indirect
- Moving toward more active Pharmacovigilance
  - PSURS
  - Post marketing studies
  - Registries
  - Risk Management plans (periodicity driven by risk)
  - Improved communication



6

## Periodic Safety Update Reports - PSURs

- Present worldwide safety experience of a medicinal product at defined times post-authorization:
  - Report all relevant new safety information;
  - Relate to patient exposure;
  - Summarize market authorization status in different countries
  - Any significant variations related to safety;
  - Create periodically the opportunity for an overall safety re-evaluation;
  - Indicate whether changes should be made to product information in order to optimize the use of the product.



7

## Two Phases of Safety Reporting

### 1. Development / Premarket

- ADR reports
- Special reports of unexpected clusters
  - DSMBs, Clinical Trial Steering committees, REBs;
- DSURs
  - Periodic safety reporting during clinical trials (modeled after the PSUR for marketed products).

### 2. Premarket / Marketed

- PSUR
  - Periodic Safety Update Reports
- Pharmacovigilance Planning



8

Global Perspective

## Pharmacovigilance just as drug development, is an Iterative process → Life Cycle

- Starts with discovery/identification of a molecule
- Screening in animals
  - PD, PK, Toxicology
- Is it safe for humans?
- Phases (1,2,3) of testing start
- Submission for marketing in a 'given indication'
- Other Indications, Conditions of Use – under development
- Benefit Risk assessment depend on data and indication
- Safety information builds with time
- Principles of Pharmacovigilance Plans
  - Life-cycle and Science-based approach to risk documentation, effective, harmonized, collaboration between regulators and industry



9

Global Perspective

## MedDRA

### Medical Dictionary for Regulatory Activities

- Standardized terminology for classification, retrieval, presentation and communication of medical information
- 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



10

# ICH

Harmonisation of regulatory requirements pioneered by the EU  
Formed at a meeting in April 1990 comprised of :

- **Six Parties** that are directly involved, EU, EFPIA, MHLW, JPPA FDA and PhRMA
- **Three Observers**  
WHO, CANADA and the EFTA, (represented by Swissmedic, Switzerland)
- **IFPMA**




11

Global Perspective

## ICH - Efficacy Guidelines (Clinical Safety)

E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E2E	Pharmacovigilance Planning
E2F	Development Safety Update Report



12

## Regional Pharmacovigilance programs

- MedWatch – FDA
- EudraVigilance – EMEA
- CanadaVigilance
- Early-Phase Post Marketing Vigilance (EPPV) Japan



13

## US FDA Model

- US FDA does not require RMPs with drug submissions for all products.
- FDA provides guidance documents to industry that focus on risk assessment and minimization during different stages of a drug's life cycle and gives direction regarding the development, implementation and evaluation of risk management activities.
- The US FDA will focus on products that pose an unusual type or level of risk. The proposed legislation is to use REMS (Risk Evaluation and Mitigation Strategies) that would require manufacturers to submit RMPs.



14

## European Medicines Agency Model

- The legislation requires that an RMP (Risk Management Plan) be submitted to regulators for (almost) all new products from MAHs.
- The EMEA states:
  - RMP submitted with applications for new medicines and generic products
  - When there is a significant change in conditions of use for an authorized product
  - When a safety concern is identified
  - When requested by a national regulator
  - The EMEA focus is on an RMP on activities that take place after a drug is marketed.



15

## 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)
- Radiopharmaceutical drugs
- Natural health products



16



## Adverse Reaction Reports

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



17

## Reporting to Canada Vigilance

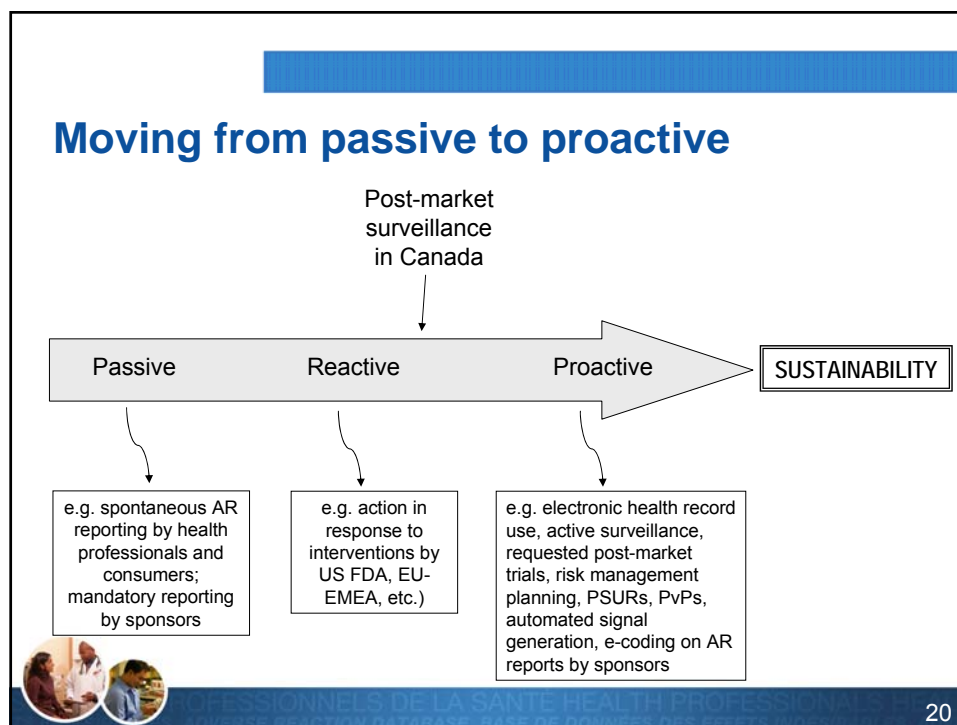
- Adverse reaction reporting form
  - Available Regional/National Offices, MedEffect website, Compendium of Pharmaceuticals and Specialties (CPS)
- Submit by fax or mail
- On-Line 

[www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
[www.santecanada.gc.ca/medeffet](http://www.santecanada.gc.ca/medeffet)
- Toll Free Telephone and Fax
- Verbal reports accepted
- Postage paid mail



18

		Target Audience	
		Public	Health Prof. / Hospitals
Responsibility for Issuance	HC	<ul style="list-style-type: none"> <li>• Public Warning</li> <li>• Public Advisory (PA)</li> <li>• Health Product Recall Notice</li> <li>• Foreign Product Alert (FPA)</li> <li>• Information Update</li> <li>• It's Your Health (IYH)</li> <li>• Fact Sheets and Backgrounders</li> </ul>	<ul style="list-style-type: none"> <li>• Health Canada Issued Health Professional Communication – Dear Health Care Professional Letter (HPC_DHCPL)</li> <li>• Health Canada Issued Health Professional Communication – Notice to Hospitals (HPC-NtoH)</li> <li>• Canadian Adverse Reaction Newsletter (CARN)</li> </ul>
	MAH with HC	<ul style="list-style-type: none"> <li>• Industry Issued Public Communication (MAH-PC)</li> </ul>	<ul style="list-style-type: none"> <li>• Industry Issued Health Professional Communication – Dear Health Care Professional Letter (HPC-DHCPL)</li> <li>• Industry Issued Health Professional Communication – Notice to Hospitals (HPC-NtoH)</li> </ul>



## 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

### Oct 2006 – Contract signed with ArisGlobal

- Products/services are used by industry including 9 pharmaceutical companies
- Participation in regulatory activities such as FDA's e-Prompt group, EMEA's joint working groups, MHLW's E2B Pilot
- Currently working on the implementation of a French language version of their software at the French Regulatory Agency (l'Agence française de sécurité sanitaire des produits de santé (AFSSAPS))
- Currently in Implementation Mode

### Integrated and complementary suite of 3 applications which include:

- Core application
- Signal detection tool
- ESTRI gateway module



21

## Implementation of Canada Vigilance Database is a 2 phased approach:

- **Phase 1:**
  - Implementation of core product – March 2008
  - Data Migration
  - Testing, Validations etc. of product & data
- **Phase 2:**
  - Electronic Reporting by Market Authorization Holders – 2009
  - Communication with stakeholders
  - Establish technical interface protocols
  - Establish small manufacturer reporting interface
  - Reporting requirements
  - Pilots to validate



22

## Consumer Reporting Form

- Project to develop form is underway and usability testing of form to take place February/ March 2008
- Guideline document to be developed



23

## Signal Detection: Adverse Reaction Data

- Reports vary widely in quality, accuracy, and completeness
- Each report represents the suspicion, opinion or observation of the individual reporter i.e. rarely proven associations
- Significant under-reporting domestically and internationally
- Cause and effect relationships have not been established in the vast majority of reports submitted
- Population exposure data often unavailable
- AR may be result of non-compliance of patient, medication error, or other system factors
- May resemble progression of disease



24

## Challenges

### Surveillance Programs for Health Products

#### Health Canada

- Medical device adverse incident reporting
- Acute transfusion reaction monitoring, blood and blood components
- Cells, Tissues and Organs reporting system
- Canada Vigilance: Monitoring system for spontaneous adverse reaction and medication incident reporting for pharmaceuticals, biologic and biotechnology products, natural health products (dietary supplements)
- Monitoring for veterinary drugs

#### Public Health Agency of Canada

- Preventive vaccines surveillance (scheduled immunization, travel, flu)
- Transfusion Transmitted Injuries Surveillance System
- CJD surveillance program



25

## Challenges

### Increased expectations

- **Pharmacovigilance (PV) depends heavily on collaboration**
  - Reach to health care professionals through risk communications has limitations (passive)
- **Operations in need of better integration**
  - Currently Pre and Post Market regulatory structure is in separate organizations - not conducive to life-cycle management
  - Roles & responsibilities need updating.
- **Public scrutiny of PV is higher than ever**
  - Surveys indicate increased need for transparency and openness
  - Expectations for public input and participation in defining major orientations
- **Adverse Reaction monitoring, detection, assessment and risk mitigation more comprehensive due to the sophisticated capabilities offered by modern technology**
  - Our IM/IT needs better integration



26

## Challenges

### Health Canada is developing a RMP Model

- The proposed RMP Approach would involve a regulatory standardized and systematic review of Pharmacovigilance Plans, a document outlining the product safety specifications and proposed pharmacovigilance activities and resulting data/information.
- Proposed RMP Program would be a hybrid of the current Canadian Status Quo and a Canadianized version of the EMEA Model.



27

## Challenges

### Pharmacovigilance Regulatory Authority Issues

- HC dependent on the voluntary submission of adverse reactions (ARs) by health professionals, manufacturers and the public.
- Manufacturers (Market Authorization Holders-MAHs) must report ARs if they have serious or serious unanticipated impact on health.
  - they are not obliged to report on evolving global knowledge and experience with marketed health products
- Canada is working towards the use of complementary information sources (eg. PSURs, PVP) and not yet harmonized with international best practices.
- No authority to compel additional post-market studies/data, labelling changes or risk communication issuance



28

## Challenges

### Broader Regulatory Issues

- While Canada's health and safety regime has served Canadians well, it requires modernization:
  - More complex products, more rapid innovation to market, new source countries
  - Consumers want more choice and involvement
- Canada's health protection system was developed in an earlier era
  - Food and Drugs Act, 1953
  - International counterparts (US, European Union, Australia) have moved to update their health and safety regimes
- Modern legislation is required to successfully implement Canada's Food and Consumer Safety Action Plan



29

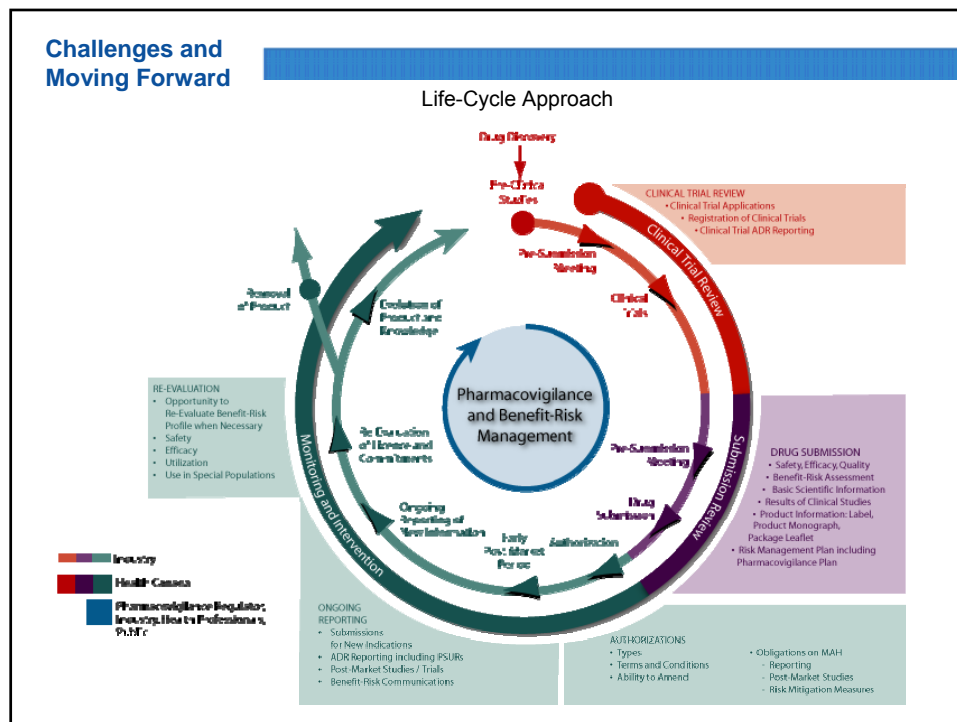
## Challenges

### Modernizing the Food and Drugs Act (Bill C51)

- Health Canada proposes a comprehensive modernization of the *Food and Drugs Act* that anticipates the present and future needs of Canadians
- Amendment updates will consist of
  - Life-cycle approach to regulating drugs
  - Mandatory reporting
  - Compliance and enforcement
  - Openness and transparency
  - Food safety



30



## Challenges

### Defining Confidential Business Information (CBI)

- **Issue:** The lack of a definition and framework to define CBI has led to inconsistent disclosure practices and has hampered Health Canada's efforts to be open and transparent.
- **Proposal:** To define a framework for how to assess CBI in legislation.
- **Safeguards:** The framework would be consistent with the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and would respect Canada's obligations under the North American Free Trade Agreement (NAFTA); other federal statutes; and regulatory frameworks of other jurisdictions.
- **Regulatory Amendments:** For greater certainty, regulations will be used to define: the types of information that are not considered to be CBI; when information ceases to be CBI; and, the timing and conditions under which such information might be disclosed.





## Challenges

### Sharing information with other governments and organizations

- **Issue:** Health Canada has actively pursued strong partnerships with key regulatory counterparts to facilitate information sharing on the safety and/or efficacy of health products, food and consumer products. Some countries are reluctant to exchange information with HC, including CBI, without specific legislative authorities and corresponding safeguards.
- **Proposal:** The Department is seeking an authority to enable the exchange of information with its regulatory counterparts in other jurisdictions.
- **Safeguards:** Information disclosure could be done through signed confidentiality agreements.
- **Regulatory Amendments:** The Department does not foresee the need for regulations with this proposal.
- **Policy Instruments:** Memorandum of Understanding



33

## Conclusions

- The shift from pre-market review to assessing and managing the risks and benefits of products throughout their entire life-cycle is good for all stakeholders (MAH, Regulators and the consumer).
- Canada is moving forward to modernize and harmonize their Regulations to enable effective Drug Regulation and Pharmacovigilance in line with the best practices globally.



34

# Thank You

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