Evolution of Pharmacovigilance in Canada with a focus on Risk Management Plans

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Caveat statement

The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the Government of Canada.

Looking Back

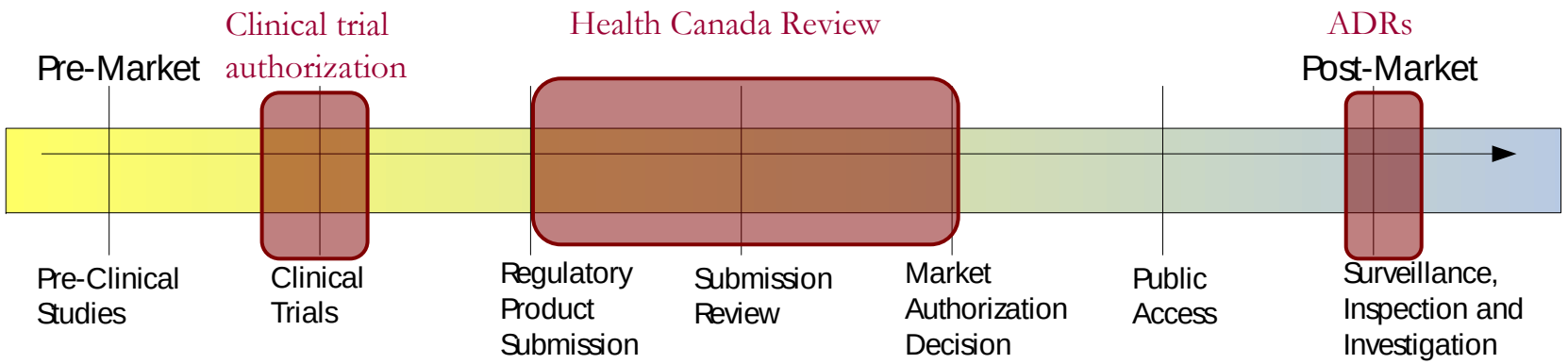
- 1960s thalidomide risk.
- Repeated occurrence of unexpected, serious adverse reaction once drug is on the market.
- Increased use of medicines to treat chronic conditions and rise of “blockbuster” drugs with large market shares exposed patients to unanticipated risks.
- Pre-market regulatory systems are recognized as incomplete to fully assess a drug safety profile: brief duration of RCTs, small subject numbers, etc.
- Potential significant off-label prescribing.

Pharmacovigilance in Canada

- 1990s CADRIS was launched
  - 2007 “Canada Vigilance” became Health Canada’s post market surveillance program.
- 2002 MHPD was created
- MedEffect Canada was launched in 2005 to:
  - Report an adverse reaction or side effect;
  - Provide centralized access to obtain new safety information on drugs and other health products.

Historic System: Licensing Model

- Point-in-time approach
- Discrete, defined Health Canada involvement in lifecycle



=Health Canada's current regulatory authority

Reality check

- Pharmacovigilance is the science of collecting, monitoring, researching and evaluating information on ADRs to identify and prevent harm.

- Reliance on spontaneous reports only captures 1/10 % of ADRs; longer the ADR's relationship to medicine goes unrecognized - more public is exposed to unacceptable harm*.

- Regulatory challenges in pharmacovigilance:
  - Goal of ensuring safety must be balanced with need for timely access to medicine
  - Limited access to healthcare databases
  - Perception of conflict of interest in industry funded studies
  - Compliance with post-market commitments is challenging; limited post-market regulatory authority

*Hazell and Shakir, 2006

Information Gathering, Monitoring and Signal detection

Current Practice

•Spontaneous voluntary reporting by health care professionals and consumers

•PSURs submitted by industry

•Capacity to detect and prioritize signals for domestic ADR reports, but limited by incomplete info.

Evolving Practice

Risk communicate about marketed health products that enable prompt interventions at point-of-care

Compile information from various sources; shift to more data analysis

Increase interactions with internal and external stakeholders

Strengthen mechanism for obtaining external advice and public input

Become more pro-active and focus on preventing harm in addition to identifying harm

Evolving Practices in Pharmacovigilance

Risk Management and Intervention

Current Practice

•Interventions limited by lack of regulatory authority

•MedEffect Canada website and e-notice usage are increasing as vehicles for communicating risk information

Evolving Practice

•Strengthen regulations to support requests that industry conduct post-market studies and assessments of real-world risks/benefits of products

•Implementation of Risk Management Plans in Canada.

•Recognized initiative to increase transparency, independence and standards for post-authorization studies.

•Outreach

Recent Progress in Pharmacovigilance

- Drug Safety and Effectiveness Network (DSEN)
  - Support product life-cycle approach to drug regulation
  - Provide additional evidence for use in ongoing risk-benefit assessment once a drug is on the market
  - Ability to commission more publically funded research

- Evaluating Effectiveness of Health Product Risk Communications (EERC) Initiative

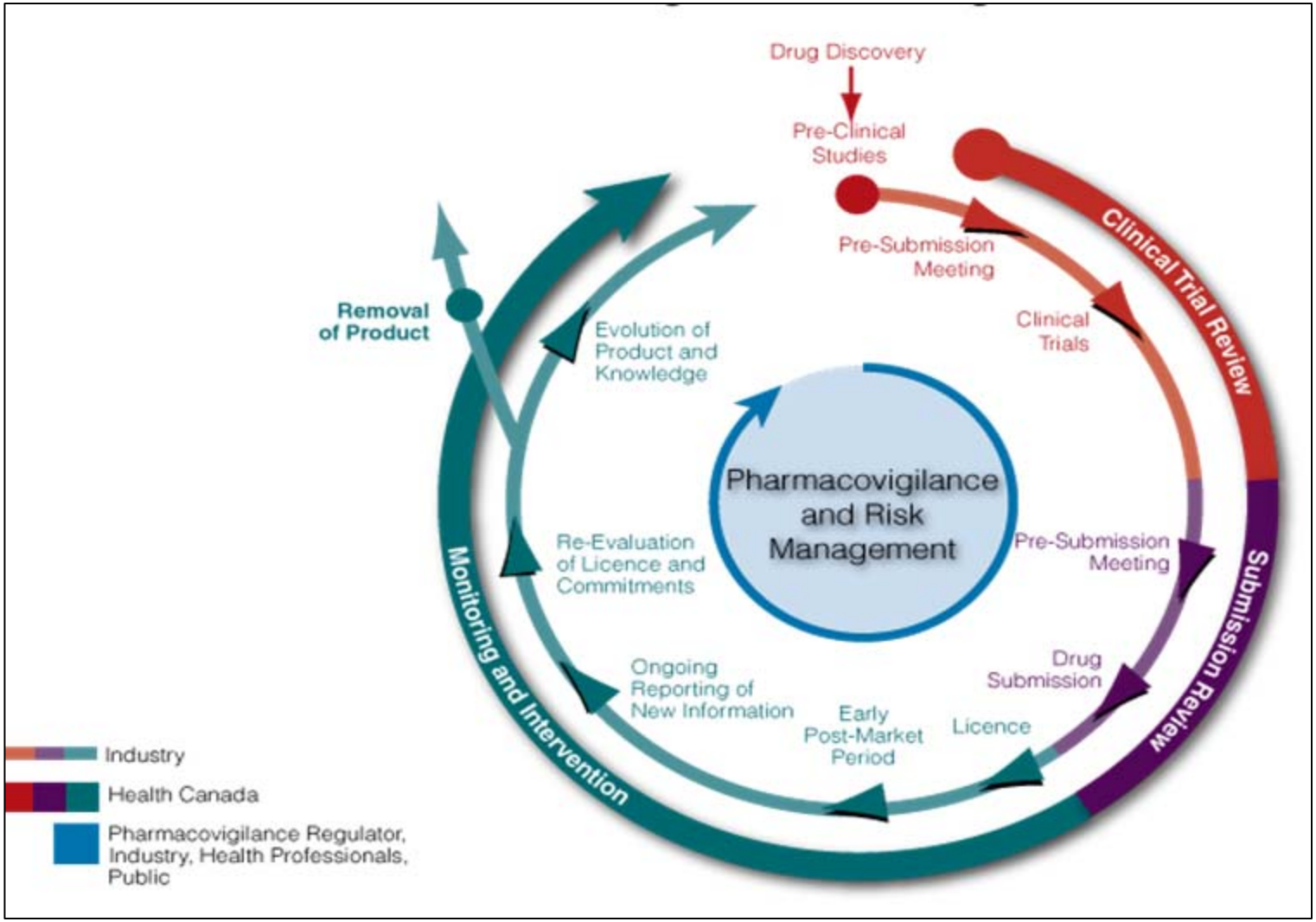
- C.0.016 Amendment
  - **C.01.018.** (1) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister an issue-related summary report.

Recent Progress in Pharmacovigilance

- Increase International Collaborations
  - 4-way Pharmacovigilance Teleconference with US FDA, TGA, MedSafe NZ, Singapore's HSA and Health Canada
  - Observer status at European Union Pharmacovigilance Working Party meetings (EU-PhV)
  - Foreign review pilot project

- Develop proactive surveillance systems through signal detection working groups:
  - Industry/ premarket identified safety issues
  - Foreign agency identified safety issues
  - Safety issues identified from the scientific/ medical literature
  - CanadaVigilance based safety issue identification

A life cycle approach to Regulation



Risk Management Plan - Background

- Notice posted on February 2009
- Implementation for drugs, biologics and biotech-derived products for human use
- EMA-RMP format suggested
- Accepted in other format (i.e. FDA REMS for risk minimization) but needs to covers similar essential elements
- Guidance rather than regulation

Risk Management Plan - Purpose

- Risk Management Plans will:
  - Describe what is known and not known about the safety profile of a medicine
  - Plan how to characterise further the safety profile of the medicine
  - Put in place measures to prevent or minimise risks associated with the product and assess the effectiveness of those interventions

- Risk Management Plans will not:
  - Lower safety standards for drug approval
  - Eliminate risk associated with therapeutic products

Risk Management Plan – Solicited

RMPs with a submission are requested for:

- NAS (except if new salt)
- all biologics including subsequent entry biologics
- products withdrawn from the market due to safety concerns which are being re-introduced on the Canadian market
- emergent post-market safety signal
- generic products, when there is a RMP with active risk minimisation measures in place for the innovator. Generic sponsor's RMP implementation approach can vary from that of the innovator.
- Other situations

Risk Management Plan – Solicited

- For marketed product, RMPs may be requested when:
  - A new serious safety issue is identified
  - There is a substantial change in indication that may be associated with a serious safety risk
  - A new serious safety risk is identified for a similar product in the class
  - Other situations

- Unsolicited RMPs are reviewed when:
  - They are related to an emergent-post-market safety signal
  - Major labeling safety update
  - Other situations

Risk Management Plan – Sections

Risk Management Plan (EMA approach):

- **Safety Specification**: a summary of the known important safety information about the drug and a means to identify gaps in knowledge

- **Pharmacovigilance Plan**: describing actions for safety concerns that have been identified or potential safety concerns which may arise

- **Risk Minimization Plan**: provides proposals on how to minimize the risks that have been identified in a real world situation (when needed)

Accomplishments

- Constant improvement:
  - In quality of RMPs submitted by drug companies
  - In internal review capacity (expertise and staff training)

- Development of SOPs, review performance targets and collaboration processes with TPD

RMP Review: Pharmaceuticals (1)

RMP	2009-2010	2010-2011	2011-2012
Associated with NDS	7	19	37
Associated with S/NDS	8	1	2
Post-market Solicited	8	4	3
Post-market Unsolicited	3	1	0
Total	26	25	42

RMP Review: Pharmaceuticals (2)

Recommendations	2009-2010	2010-2011	2011-2012
Labelling changes	6	9	12
Risk minimisation measures (mainly study results & PSUR review requests)	14	14	17
Revise and resubmit RMP	7	5	13
Total	27	28	42

RMP Review: Biologics (1)

RMP	2009-2010	2010-2011	2011-2012
Associated with NDS	9	1	16
Associated with S/NDS	7	2	6
Post-market Solicited	14	18	21
Post-market Unsolicited	1	2	1
Total	31	23	44

RMP Review: Biologics (2)

Recommendations	2009-2010	2010-2011	2011-2012
Labelling changes	8	5	17
Risk minimization measures (mainly study results & PSUR review requests)	15	10	25
Revise and resubmit RMP	9	5	11
Clarification requests	3	1	15
Total	35	21	68

Challenges

- Not Submitting the most up to date version of the RMP

- Most RMPs are submitted in EMA format but lack Canadian specific sections
  - Epidemiology of the medical condition in Canada
  - Timelines for submission of updated RMP documents
  - Post-market experience in Canada
  - Utilization of the available-online Canada vigilance database

- Failure to identify measures to evaluate effectiveness of risk minimization strategies

Challenges

- Off-label use often not addressed
- RMP is not built a stand alone document (keep in mind the document will be reviewed by a separate group)
- Lack of inclusion of relevant risks under missing information (ie., long-term safety, use in patients with renal impairment, dose modification, use in patients with co-morbid conditions)
- Generics
  - Multiple forms of risk minimization measures for same active substance

International Developments – FDA - 2012

- FDAAA 2007 gave the FDA the **authority to require postmarket studies** of drug safety concerns and drug labeling changes when new drug safety information is identified

- FDA released a **guidance document for industry** to determine extent of safety data collection (Feb 2012).

- FDA April 2012 report: **FDA strengthens monitoring of post-approval drug safety**
  - Describes new scientific tools and enhanced capabilities that give the same priority to postmarket drug safety monitoring as to premarket drug review
  - Enhanced quality, accountability, and timeliness of postmarket drug safety decisions, and public communication of this information is more effective
  - Up to April 2012**,** FDA has required 64 complex REMS
  - FDA sentinel system to access electronic healthcare records with a goal of 100 million patients by 2012.

International Developments- EMA- 2012

Past RMP structure

Part I

Safety Specification

Part II

Pharmacovigilance Plan

Part III

risk minimisation

Modified RMP structure

Part I: Product overview

Part II: Safety Specification (subsection with modules 1-V111)

Part III: Pharmacovigilance Plan

Part IV: Studies on effectiveness and long-term efficacy

Part V: Risk Minimisation Measures

Part VI: Summary of the RMP

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International Developments- EMA- 2012

- Document the need for efficacy studies and maximise the benefit risk balance of the product for the individual patient and for the target population as a whole and to facilitate integration of benefit risk planning.

- Part IV **Studies on effectiveness and long-term efficacy**
  - Summarise efficacy and basis for this – i.e., studies and endpoints
  - Short review of where fits into therapeutic options
  - Discuss robustness of endpoints and need for effectiveness and long term efficacy
  - Applicability of efficacy studies to all patients in target population
  - Consideration of studies to determine which patients will benefit the most

- Part VI **Public Summary of the EU-RMP**
  - Public Summary of the RMP aimed at lay people

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Conclusions

- Intelligent Risk Management Planning is changing the environment of drug safety – more information & better access to it.
- Can be used as a powerful tool for risk assessment and (potentially) risk minimization.
- It is an evolving and dynamic document.
- Dialogue among the parties involved is important.
- Everyone is still learning
  - Does one size fits all?
  - Keep what has worked, and continue to change the less good

Overall- Looking Ahead

- Drivers that Health Canada needs to keep in mind
  - Expectations from Health Care Professionals and consumers
  - International Collaborations
  - Open government initiatives and HPFB strategic plan
  - Risk prioritization
  - New technology and data sources
  - 2011 Auditor General Report

Overall- Looking Ahead & Wish list

- Increased transparency
- Increased public awareness in MHPD's post-market surveillance contribution to the healthcare system
- Enhanced International activities and outreach
- Dynamic Benefit/Risk assessments as new information emerges
- Stronger regulations and increased compliance
- Enhance working relationship with provincial and territorial governments
  - leveraging provincial healthcare databases
  - evaluate safety and effectiveness under the conditions in which the drug is used

Overall - Looking Ahead

* Canadian Agency for Drugs and Technologies in Health

Thank you!