

# Health Products and Food Branch

Your Health and Safety - Our Priority

## *Marketed Health Products Directorate*



## **Future Directions in the Review of Post-Market Safety Data, Sources of Evidence and Risk Assessment Tools**

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Health  
Canada

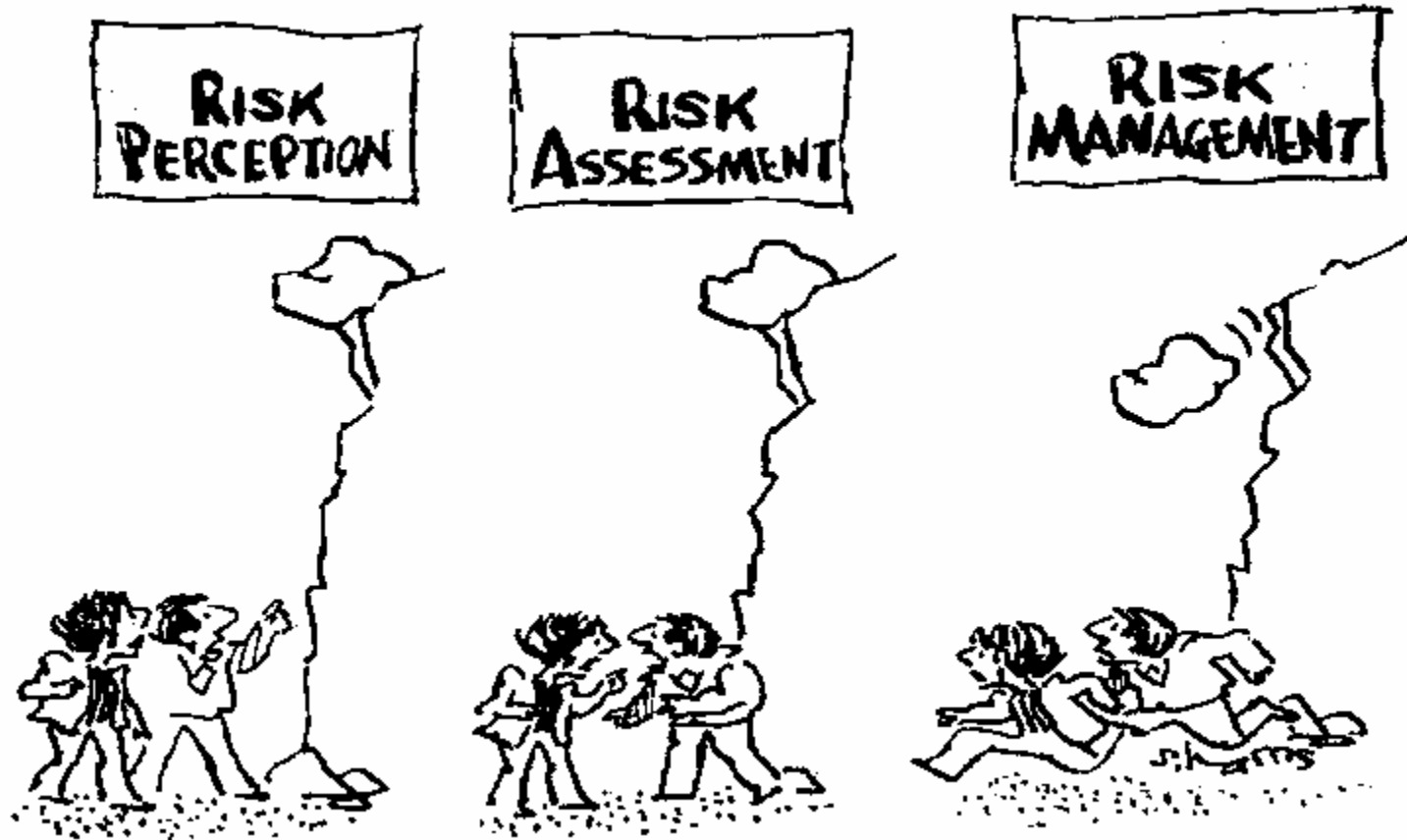
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# Outline

- Principles of risk management
- Current status
- Future Trends
- Conclusions

# Principles of Risk Management



# Current Status

- Core Activities
- Types of data
- Sources of Evidence
- Assessment tools/techniques

# Core Review Activities Flow Chart

## Monitoring Inputs

**Environmental Scanning:**

- Media
- Medical Literature

**Regulatory Agencies:**

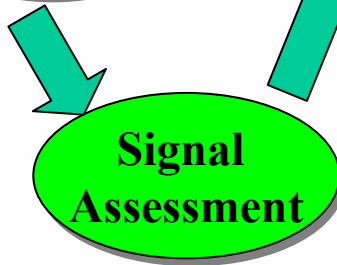
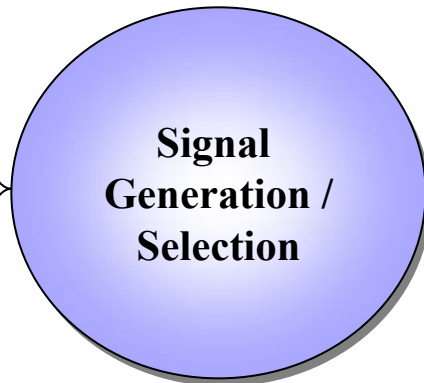
- Reporting databases
- Risk Communications

**Companies:**

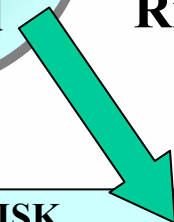
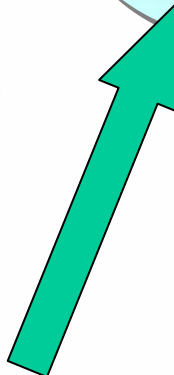
- Phase IV Studies
- PSURs
- Registries
- Communications

**Health Canada:**

- Spontaneous Reports (CADRMP)
- WHO-Vigimed



## Risk Management Capacity



# Current Data Types

- Spontaneous Adverse Drug Reaction (ADR) data
- Case reports/case series data
- Epidemiological “in real world setting” data
- Experimental clinical data

# Current Sources of Evidence

- **Pre-market:**

- RCTs

(Scientific Literature  
and/or MAHs)

- Clinical Trial ADRs
- Meta-analysis

- **Post-market:**

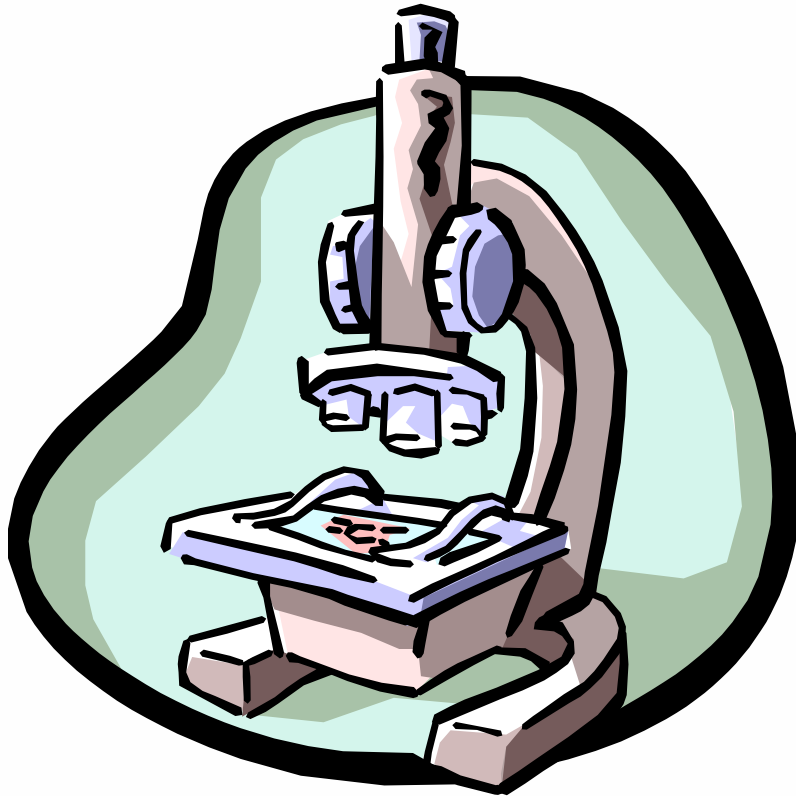
- Spontaneous ADR reports (CADRMP)
- PSURs/Safety Summaries
- Comparative Observational Studies
- Registries
- Post-market safety studies
- Scientific/medical lit

# Risk Assessment Tools

- **Spontaneous sources:**
- Case series analysis
- Causality Assessment
- Reporting rates
- Effects of exposure dose, duration, time, demographic factors, comorbid conditions, concomitant drugs, sub-populations
- Factors strengthening associations: rechallenge, dechallenge, absence of alternative causes.



# Risk Assessment Tools



- Non-Spontaneous Sources:
- A) Comparative observational studies
  - Cross-sectional
  - Case-control
  - Cohort studies (retrospective and prospective)

# Risk Assessment Tools

- Cross-sectional studies:
  - Survey on a population of patients at a single point in time
  - Evaluation of a safety signal from spontaneous case reports
  - Condition or AE prevalence
  - Crude estimate of the association between exposure and outcome

# Risk Assessment Tools

- Case-control studies:
  - Comparison of the exposure status using the Odds ratio (or others) – estimate of the relative risk of events among the exposed versus the non-exposed
  - Stratification of population of interest
  - Identification of risk factors
  - Limitations: selection bias, retrospective, confounding variables

# Risk Assessment Tools

- Cohort Studies:
  - Comparison of exposed patients to unexposed patients based on drug use and followed over time
  - Incidence rates of AEs in addition to the relative risks or Odds Ratio of AEs
  - Limitations: Same as case-control studies

# Risk Assessment Tools

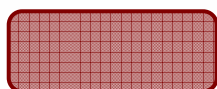
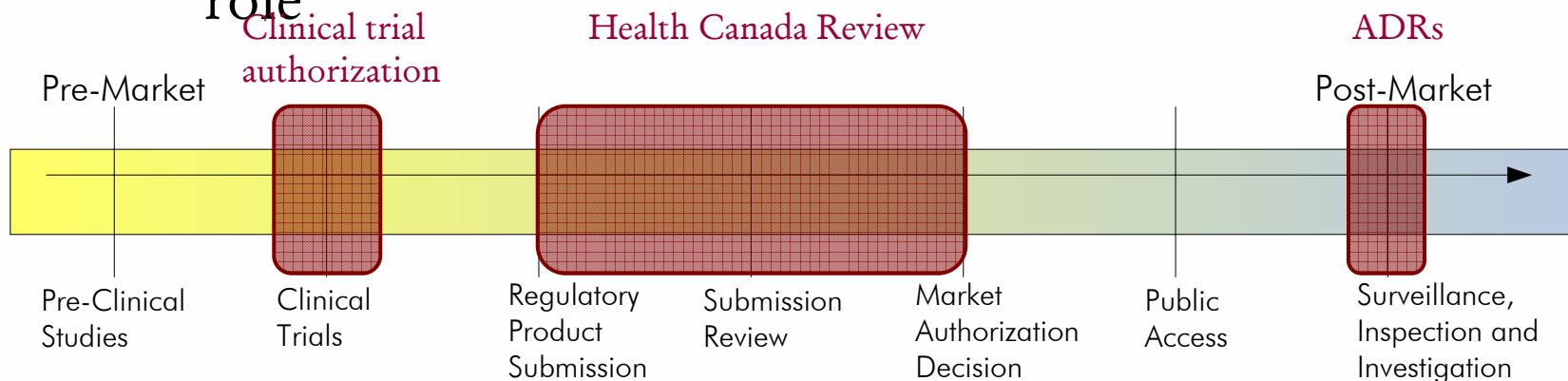
- B) Registries:
  - List of patients sharing a specific exposure e.g. Clozapine drug registry
  - Registry patients can be included in a cohort study
  - Limitations: tailored to specific objectives, data not necessarily useful for regulator

# Risk Assessment Tools

- C) Database studies:
  - Integration of provincial data
  - Drug utilization data alone, and associated with health outcomes data
  - Limitations: confidentiality, operational, political all of which limit access
  - E.g. RAMQ, Saskatchewan HSD

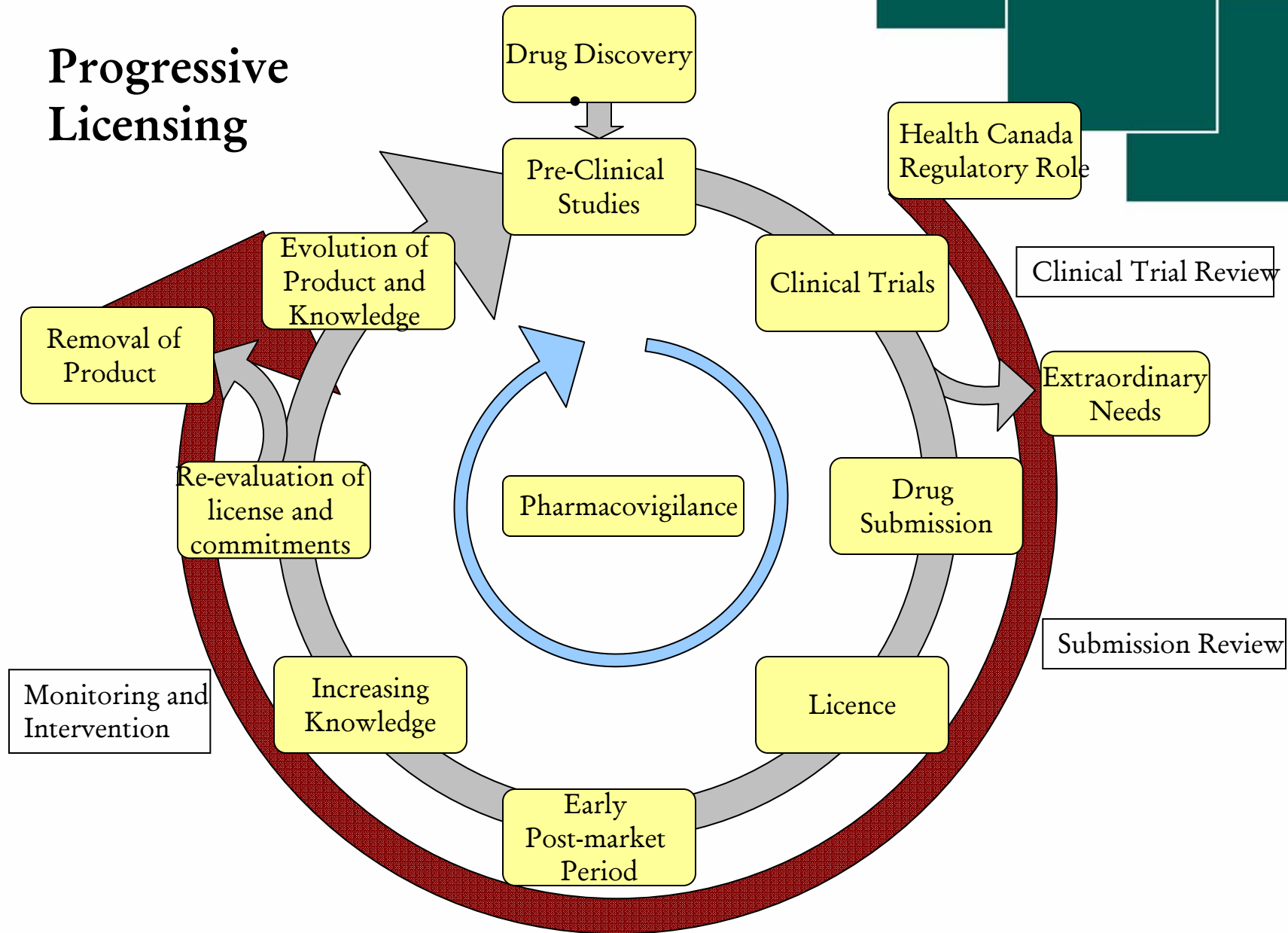
# Current Linear Licensing Model

- Point-in-time approach
- Discrete, defined Health Canada involvement in lifecycle
- Little regulatory force outside of defined role



= Health Canada's Current Regulatory Authority

# Progressive Licensing



# Future Trends

- Risk Management Plans (EMEA)
- Strategies to reduce patient and population risks
- Components:
  - **Safety specifications**
  - **Pharmacovigilance Plan**
  - **Evaluation of need for risk minimization measures**
  - **A risk minimization plan including evaluation of performance**

# Future Trends

- US FDA:
- Good Pharmacovigilance Practices and Pharmacoepidemiologic assessment
  - Safety Signal Identification
  - PE assessment and safety signal interpretation
  - PV plan development
    - Routine PV plans
    - Enhanced PV plans

# Future Trends

- US FDA:
  - Development and use of risk minimization action plans (RiskMAPs)
  - Targets one or more safety related outcomes
  - Provides tools to achieve these goals
  - Selectively used safety action plan
  - Includes evaluation step

# Future Trends in Canada

- Implementation of ICH E2E
- Pharmacovigilance Planning
  - Documents known risks and the potential for unidentified risks
  - Plan to collect post-market safety data to demonstrate safety and identify harm

# Future Trends in Canada

- Consultation with the public and other stakeholders
- Public Forum (e.g. COX-2s, Breast Implants)
- Expert Advisory Panels (e.g. Cox-2s)
- Expert Advisory Committee on HPV
- Academia

# Future Trends in Canada



- Implementation of interim and permanent internal processes for the review of PvPs
- FDA vs EMEA vs Health Canada
- Pre vs post market role
- Legal implications

# New Pharmacoepidemiologic Tools

- Large, simple safety trials
- Solicited reporting
- Phase IV clinical trials
- Drug utilization studies

# New pharmacoepidemiologic tools

- Solicited reporting:
  - Derived from organized data collection systems
  - Include clinical trials, registries, post-approval patient use programs, patient support and disease management programs, surveys of patients or health care providers, information gathering on efficacy

# New pharmacoepidemiologic tools

- Phase IV study designs:
  - Post-phase III continuation trial (<500)
  - Phase V effectiveness trial (250-1000)
  - Prospective Cohort (500-1000+)
  - Retrospective Cohort (100-500+)
  - Patient Registry or Longitudinal Observation Study (300-10000)

# New Pharmacoepidemiologic Tools

- Phase IV studies (cont'd)
  - Large computerized databases and record linkage (>10000 to millions)
  - Novel Designs are required

# New Pharmacoepidemiological Tools

- Drug Utilization Studies:
  - Qualitative
  - Quantitative

# Opportunities List

- Novel design Phase IV studies
- Registries
- Provincial, national and international databases



# Conclusions

