Advance Topics in Pharmacoepidemiology

• Risk Management

2012 Mid-Year ISPE Meeting
Miami, April 21-23, 2012

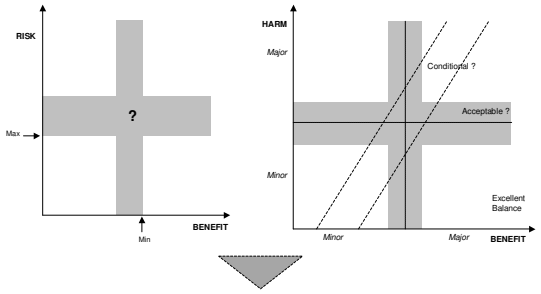
Ariel E., Arias MD, PhD
- *Fac. Pharmacy; Université de Montréal*
- *Biologics & Genetic Therapies Directorate, Health Canada*

Conflict of Interest Declaration

• The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the *Université de Montréal* or the *Government of Canada.*

• No other conflict of interest to declare.

Benefit – Harm Profile ?



Risk Management

Rationale for Risk Management & Miminisation

- 130 pharmaceuticals removed over last 4 decades (Tsinitis et al. Drug Safety 2004; 27:509)
  - ⅓ within 2 years of marketing
  - ½ within 5 years of marketing
- Authorization based on specified indication at time of filing (punctual and limited benefit/risk assessment)
- Failure of product labeling and risk communications to resolve new risk issues (e.g., Cisapride, Baycol, Vioxx)
- Modern pharmacovigilance:
  - Proactive and starting earlier
  - Philosophical change: Demonstrating safety rather than looking for harm

Risk Management - Definition

…a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions

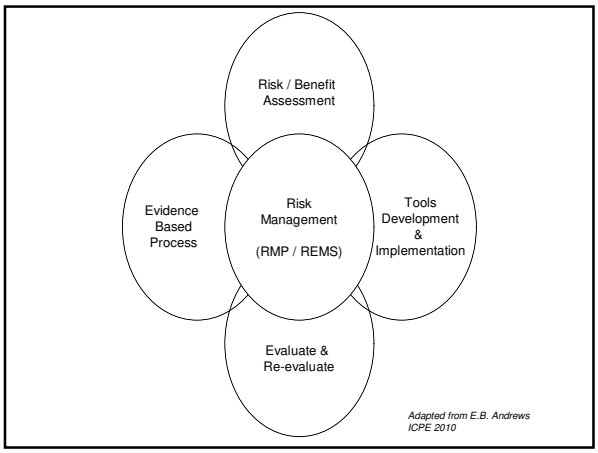
S Blackburn, ICPE 2011

…is an iterative process of (1) assessing a product's risk-benefit balance; (2) developing and implementing tools to minimize its risks while preserving its benefits; (3) evaluating tool effectiveness and reassessing the risk-benefit balance; and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the risk-benefit balance. Together, risk assessment and risk minimization form what the FDA calls *risk management.*

Risk Minimisation Activities (RMA)

Public health interventions intended to prevent or reduce the probability of the occurrence of ADRs associated with the exposure to a medicine, or to reduce their severity should they occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse reaction. These activities may consist of routine risk minimisation (e.g., product labelling) or additional risk minimisation activities (e.g., professional or patient communications/educational materials).

Appendix A in PBRER Draft Guideline ICH E2C (2012)



Adapted from E.B. Andrews ICPE 2010

PHARMACOVIGILANCE PLANNING
ICH E2E
&
PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)
ICH E2C(R2)

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 27/09/2006
Doc.Ref. EMEA/359232/2006

Annex C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU – RMP)

This template provides advice on how the data requested in the Guideline, if available, should be presented. It is anticipated that, particularly in section 1, all the information will not be available for all drugs and that the type of product and where it is in its lifecycle will affect how much information can be provided.

Overview of EU Risk Management Plan Template

Section	
1	Product information
1	Safety Specification
2	Pharmacovigilance Plan
3	Evaluations of the need for risk minimisation activities
4	Risk minimisation plan
5	Summary of the EU-RMP
6	Control person details
Annex 1	Interface between EU-RMP and Pharmacovigilance *To be provided in electronic form only*
Annex 2	Current (or proposed if initial EU-RMP) SPC, Package Leaflet
Annex 3	Synopses of ongoing and completed clinical trial programme
Annex 4	Synopses of ongoing and completed pharmacoepidemiological study programme
Annex 5	Protocols for proposed and ongoing studies in pharmacovigilance plan
Annex 6	Newly available study reports
Annex 7	Other supporting data
Annex 8	Details of proposed educational programme (if applicable)

Guidance for Industry

Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comment and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

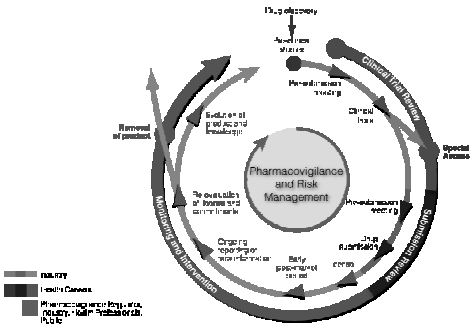
For questions regarding this draft document contact (CDER) Kathleen Frost 301-796-2380, or (CBER) the Office of Communication, Outreach, and Development (OCOD) at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2009
Drug Safety

Health Canada / Santé Canada

Progressive Licensing Model



When to file a RMP / REMS ?

Typically

- ❑ With the application for drug licensing for innovative products (new chemical entities)
- ❑ Generics or biosimilar medicinal products for which a risk has been identified for the reference product
- ❑ Significant change to the MA
  - New pharmaceutical form
  - New route of administration
  - New indication/patient population
- ❑ *By request from the regulatory authority*

Structure of the EU-RMP

Part I

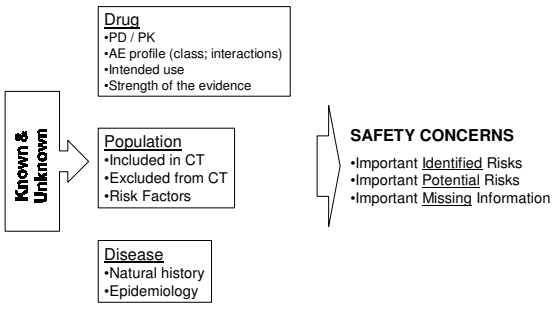
- ❑ Safety specification
- ❑ Pharmacovigilance plan (PVP)
  - Routine pharmacovigilance activities
  - Additional pharmacovigilance activities

ICH E2E

Part II

- ❑ Evaluation of the need for RMAs
- ❑ Risk minimisation plan
  - Routine RMAs
  - Additional RMAs including:
    - Objective and rationale
    - Proposed actions
    - Success criteria
    - Proposed review period

Safety Specification



Pharmacovigilance Plan (PVP)

SAFETY CONCERNS

❑ Routine PV activities

- •ADR reporting and follow up
- •Expedited ADR reporting
- •Signal detection
- •Signal assessment
- •PSUR (PBRER)

❑ Additional PV activities

- •Active surveillance (e.g. PEM)
- •Enhanced monitoring (e.g. claims DB, e-medical records)
- •Additional studies
  - •Observational (Phase IV) e.g. Case-control, Cohort, Record Linkage, Drug Utilisation, etc
  - • Clinical Trials
  - • Pre-clinical studies

Risk minimisation plan

Safety Concerns: Prevent or Minimise?

Is a risk minimisation plan needed?

Routine risk minimization activities	Additional risk minimization activities
•Legal status	•Controlled distribution
•Pack Size	•Informed consent/treatment
•SPC (PM)	•Patient monitoring/screening
•Package leaflet	•Pregnancy prevention programme
•Labelling	•Educational material
	•Registry
	•Special packaging/labels

Considerations for the PVP and RMA

Safety Specification

Safety Concerns?

No target AE or sub-population	Potential risk, e.g., target AE or sub-population	Identified risk, i.e., target AE or sub-population
Routine PV activities?	Additional PV activities	Additional PV activities
Routine RMAs	Routine RMAs?	Additional RMAs

RMA Evaluation

Key Considerations

1)Feasibility
- Target population
- Acceptability (by all stakeholders)
- Transparency (framework for decision-making purposes)

2)Effectiveness
- Choice of source and type of metric
- Systematic and continued process of review
- Frequently done by surveys of MDs, pharmacists, and/or patients, but…
- Various DB and/or other study designs are also available

Ultimate goal and metric is product safety

RMA Evaluation – Some Metrics

Selected sources

- Cognitive testing (educational material)
- Knowledge and awareness (survey)
- Distribution tracking
- Drug utilisation studies
- Chart reviews
- Prospective observational studies with real time monitoring (e.g. lab testing & claims DB)
- Observational studies in well defined populations

Risk Evaluation and Mitigation Strategy, REMS Elements **(FDAAA, 2007)**

Before FDAAA
- Premarketing Risk Assessment
- Risk Minimization Action Plans (RiskMAPs)

REMS <u>can</u> include:
- Medication guides or patient package inserts
- Communication plans to health care providers
- Elements to ensure safe use (ETASU) that may or not be linked to some type of restricted distribution
- Implementation system

REMS <u>must</u> include:
- Timetable for submission of assessments of REMS.

REMS Elements (1)

Medication guides

- ❑ FDA approved patient-friendly labeling
- ❑ May be part or not of the REMS

Communication Plan *(EU equivalent?)*

- ❑ Aim at informing health care providers (not to patients)
- ❑ May include:
  - DHPLs
  - Dissemination through professional societies
  - Information to encourage REMS implementation
- ❑ Implementation is sometimes lead by the FDA (ANDA)

REMS Elements (2)

Elements to Assure Safe Use (ETASU)

- ❑ May include:
  - Particular training or certification for prescribing
  - Certification or pharmacies, practitioners or health care settings for dispensing *(EU equivalent?)*
  - Health care settings restrictions for dispensing *(EU equivalent?)*
  - Evidence of safe-use conditions restrictions for patients *(EU equivalent?)*
  - Patient monitoring restrictions
  - Mandatory registry enrollment

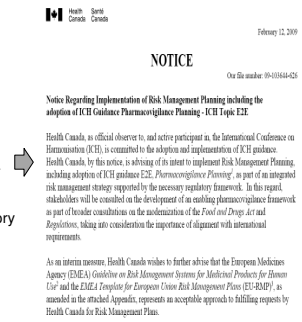
❑Are not mutually exclusive (considerable overlap)

Risk Management Planning Canadian Perspective (1)

RMP or REMS?

A harmonised risk management context?

•Their elements are common, but…
•The regulatory context (powers) differs, thus…
• Both, the science and the regulatory oversight are also under active development…



Health Canada / Santé Canada

February 12, 2009

NOTICE

Our file number: 09-103644-826

Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning - ICH Topic E2E

Health Canada, as official observer to, and active participant in, the International Conference on Harmonisation (ICH), is committed to the adoption and implementation of ICH guidance. Health Canada, by this notice, is advising of its intent to implement Risk Management Planning, including adoption of ICH guidance E2E, *Pharmacovigilance Planning*[1], as part of an integrated risk management strategy supported by the necessary regulatory framework. In this regard, stakeholders will be consulted on the development of an enabling pharmacovigilance framework as part of broader consultations on the modernization of the *Food and Drugs Act* and *Regulations*, taking into consideration the importance of alignment with international requirements.

As an interim measure, Health Canada wishes to further advise that the European Medicines Agency (EMEA) *Guideline on Risk Management Systems for Medicinal Products for Human Use*[2] and the *EMEA Template for European Union Risk Management Plans* (EU-RMP)[3], as amended in the attached Appendix, represents an acceptable approach to fulfilling requests by Health Canada for Risk Management Plans.

Risk Management Planning Canadian Perspective (2)

- Interim implementation for drugs, biologics and biotech-derived products for human use
- Request in the EU-RMP format
  - One Canadian content exception: Section 4.5.2.2: Discuss post-market experience in the Canadian context
- Accept in other format (i.e.; RiskMAP/REMS) if covers essential elements
- Guidance rather than regulation
- Collaboration between pre- and post-market assessment

Muchas Gracias !

ariel.arias@hc-sc.gc.ca