Advance Topics in Pharmacoepidemiology

• Risk Management

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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.

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Benefit – Harm Profile?

Risk Management

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Rationale for Risk Management & Minimisation

- 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)
Risk Management (RMP / REMS)

Risk / Benefit Assessment
Evidence Based Process
Risk Management (RMP / REMS)
Tools Development & Implementation
Evaluate & Re-evaluate

Adapted from E.B. Andrews
ICH 2010

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

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

Programma Learning Models
### 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

**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

**Drugs**
- PK / PD
- ADME profile (class; interactions)
- Intended use
- Strength of the evidence

**Population**
- Included in CT
- Excluded from CT
- Risk factors

**Disease**
- Natural history
- Epidemiology

**SAFETY CONCERNS**
- Important Identified Risks
- Important Potential Risks
- Important Missing Information
Pharmacovigilance Plan (PVP)

- 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 minisation plan

Safety Concerns: Prevent or Minimise?

Is a risk minisation plan needed?

Routine risk minimization activities
- Legal status
- Pack size
- SPC (PM)
- Package leaflet
- Labelling

Additional risk minimization activities
- Controlled distribution
- Informed consent/treatment
- Patient monitoring/screening
- Pregnancy prevention programme
- Educational material
- Registry
- Special packaging/labels

Considerations for the PVP and RMA

Safety Specification

Safety Concerns?

No target AE or sub-population
- Routine PV activities
- Routine RMAs

Potential risk, e.g., target AE or sub-population
- Additional PV activities
- Additional RMAs

Identified risk, i.e., target AE or sub-population
- Additional PV activities
- 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 can 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 must include:
• Timetable for submission of assessments of REMS.
Revised Electronic Reporting System (REMS)

**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 (1)**

**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)

**REMS Elements (2)**

**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...
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!

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