Risk Management in “Real Practice”

October 22, 2013

Henri CAPLAIN, MD, MS
Associate Vice-President
Head Risk Management Center of Excellence
Global Pharmacovigilance & Epidemiology
Sanofi
Disclaimer

The views and opinions expressed in this presentation are solely those of the presenter and do not necessarily reflect those of Sanofi, or any of its affiliated organizations.
Issues encountered with RMPs – Key Challenges

- Harmonization
- Workload
- Local Implementation
- Efficiency of risk minimization activities (vs. burden)
Challenges of the Harmonization

• Harmonization:
  • Harmonization across agencies (e.g. EU, national/decentralized procedures: EMA, MHRA, ANSM, INFARMED, MEB, BfArm)
  • Harmonization within agencies (Worldwide: e.g. FDA, EMA, Health Canada, TGA, PMDA)
  • Harmonization of product specific RMP in global markets
  • Harmonization of RMPs within MAHs for a same substance
  • Harmonization of RMPs within therapeutic areas at Company level
  • Harmonization across safety documents (e.g. RMP/PBRER/PSUR)
**PV & Risk Management Regulatory Landscape (Update May 2013)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>* Circular on &quot;good practices for analysis and RM plan&quot; (Nov 2009)</td>
</tr>
<tr>
<td>Australia</td>
<td>* EU guideline adopted (Nov 2008); AU RMP guidelines and TGA Q&amp;A (update Oct 2012)</td>
</tr>
<tr>
<td>Bosnia</td>
<td>* Ordinance on Method of Reporting, Collecting and Monitoring of AE to MP. (July 2012)</td>
</tr>
<tr>
<td>Brazil</td>
<td>* PV Plan and Risk Minimization Plan (Feb 2009)</td>
</tr>
<tr>
<td>Canada</td>
<td>* Adoption of ICH E2E (Feb 2009); EU template or REMS accepted</td>
</tr>
<tr>
<td>China</td>
<td>* Notification of special procedures in new drug registration (2009) – article 18</td>
</tr>
<tr>
<td>Croatia</td>
<td>* Adoption of EU guideline &amp; Template (Oct 2008)</td>
</tr>
<tr>
<td>Egypt</td>
<td>* Guideline for Marketing Authorization Holders (Jan 2012)</td>
</tr>
<tr>
<td>European Union</td>
<td>* GVP module V – RM systems (update Jul 2012)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>* Guidance Notes on Registration of Pharmaceutical Products/Substances</td>
</tr>
<tr>
<td>Indonesia</td>
<td>* Planned</td>
</tr>
<tr>
<td>Japan</td>
<td>* RMP guidance (Apr 2012)</td>
</tr>
<tr>
<td>Jordan</td>
<td>* Principles of PV System for the year 2010</td>
</tr>
<tr>
<td>Kazakhstan Russia</td>
<td>* Rules of monitoring of AEs for medicinal and pharmaceutical organizations (Nov 2009)</td>
</tr>
<tr>
<td>Korea</td>
<td>* Draft guidelines published in 2011</td>
</tr>
<tr>
<td>Malaysia</td>
<td>* Checklist for NCE and Biotechnology Products (RMP-PSUR)</td>
</tr>
<tr>
<td>Mexico</td>
<td>* Mexican Official Standard NOM-220-SSA1-2012, PV Installation &amp; Operation</td>
</tr>
<tr>
<td>Namibia</td>
<td>* National Guidelines for Medicine Safety Surveillance (Nov 2011)</td>
</tr>
<tr>
<td>Philippines</td>
<td>* Post Market Surveillance of Authorized Drug Products (FDA Circular 2013-004)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>* Adoption EU guideline &amp; Template (Nov 2009)</td>
</tr>
<tr>
<td>Singapore</td>
<td>* Guidelines for RM Plans (Apr 2011)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>* Follow EU guideline &amp; Template (Jan 2007)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>* Guidelines on RMP and Suggested Format and Contents (Apr 2012)</td>
</tr>
<tr>
<td>Turkey</td>
<td>* Guideline for RM Systems (May 2011)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>* Order No. 1005 (Dec 2011)</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>* Circular on RMP for products at time of (re)registration (Apr 2010)</td>
</tr>
<tr>
<td>United States</td>
<td>* REMS guidance for Industry (Sept 2009)</td>
</tr>
</tbody>
</table>
Main orientations of RMP regulations landscape

- SAFETY SPECIFICATIONS:
  - Risks (identified or potential), or from missing information

- EU oriented:
  - ICHE2E oriented
  - RISK ASSESSMENT Pharmacovigilance (PV) Plan
    - To further characterize/assess risks

- US-oriented:
  - RISK MINIMIZATION Plan
    - To minimize risks

NOS: Not otherwise specified
Risk Management Plan (Module 1) – Question 35 - The following should be added as important potential risks:

- Suboptimal biological activity of the chondrocytes implanted (as listed for the EU regulator);
- Risk of transmission of zoonotic disease (from porcine or bovine components);
- Risk of transmission of disease between cell cultures where no testing is performed for the infectious agent; and
- Risk of transmission of disease between cell cultures where testing is performed for the infectious agent, but where a false negative may occur (due to a window period or otherwise).
Risk Management Plan (Module 1) – Question 36 - The following should be added as “Important” Missing Information:

- Fibrotic cell migration to areas outside the target cartilage and associated reactions (even though the likelihood of this happening is remote, and given that the ACI-Maix will likely degrade over time, the migration of cells via synovial fluid and lymph may lead to an autoimmune reaction or rejection reaction).
- Use in patients with osteochondritis dissecans;
- Use in patients with chondromalacia patellae;
- Use in patients with rheumatoid arthritis or inflammatory arthritis;
- Use in patients on immunosuppressive therapy;
- Use in patients with acute traumatic injury;
- Use in patients with moderate osteoarthritis;
- Effects on fertility;
- Use in patients with cartilage defects exceeding 20 cm2;
- Use in joints other than knee joints; and
- Use in patients retreated with MACI or after treatment failure.
Harmonization: Sanofi Example

● One of the most challenging tasks is to harmonize a risk management plan
  ● For this reason, some companies have a group dedicated for Risk Management
  ● Risk Management Plans (RMPs) have become increasingly complex and required by most countries

● Sanofi started the Risk Management Group in 2007
  ● Consult with project teams for products in early development (D-RMP)
  ● Define risk management strategy
  ● Support submission-related activities
  ● Support implementation of the RMP at the local / regional levels
  ● Training on risk management concepts / content
  ● Team consists of MDs/PharmDs
Summary

● Different healthcare infrastructure in different countries
● Different ways of prescribing
● Different regulatory and legal frameworks impact local adaptation of the risk minimization plan
● Some countries require RMPs to be submitted at time of registration
  ● Many countries prefer the EU-RMP
● Risk management documents could be different, but the ultimate goals are essentially the same – patient safety
Challenge of the Workload in EU

- Huge increase of RMPs number and particularly “routine” ones: It appears every product is treated like a "new product" with the new legislation (for example developing list of risks for mature products that have been on the market for > 20 years)
- Overlap/Duplication with PSUR/PBRER (risk of inconsistencies)
- Large documents with modules/annexes (26! In EU) at different stages of update
• New RMP requirements cause a steep increase in the number of documents
  – For products without risk management beyond routine: an administrative burden with no added value?
  – How to harmonize RMPs for the same substance across all MAHs?

• Summary for the Public in lay language
  – Still no example published.
  – Template with tables, several pages: Value for the public?

• RMP requirements for new applications involving generics without risk management beyond routine
  o May become an administrative burden for no added value
Under GVP module V, there is an increased requirement to produce EU-RMPs for products which have been on the market for >10 years.

GVP focuses on newer products and limited feedback has been received on EU-RMPs submitted so far. Therefore, expectations for older products unclear.

The workload for MAHs and regulators is not insignificant & the value to patient safety is minimal when there are no risk minimisation measures other than routine.

For established non-prescription products, an appropriate benefit-risk ratio has already been demonstrated for use without intervention of healthcare professional.
Industry Proposal

• Target

  • Concise document, length & structure dictated by relevant content only.

• Proposal

  • Joint AESGP/EFPIA proposal to make EU-RMP more aligned to the stage of the product in the life cycle (similar to abridged EU-RMP for generics).
Challenge of the Local Implementation

- Local responsibility on the oversight of global
  - Communication global to local/local to global
- Adaptation of the risk minimization activities to the local situation: e.g. US REMS MedGuide vs. EU Patient Leaflet
  - Different healthcare system
  - Different medical practices
  - Different stakeholders
  - Different cultural approaches
  - Different tools (eg Website cannot be used everywhere)
  - Different resources
- Feasibility and efficiency of some minimization tools: proportional answer to the risk
- Frontier between risk educational material and promotional materiel: way of communications
Interaction between healthcare system and minimization measures

- Local healthcare system provides an environment that impact compliance of prescriber
  - Local limited regulations do not safety compliance control
  - e-Patient file, link between disease of patient and indication in SPC, or insurance system compliance control can be synergistic with minimization tools

- Example: 1.5 years after labeling changes and adequate minimization measures for a Cardiovascular drug:
  - An addition of a new contra-indication (CI), this CI is recorded in 4% of patients in Sweden, but 15% in Germany and 21% in Czech Republic
  - A restricted indication is implemented with 90% (including patients who were prescribed before implementation) in Sweden, 81% in Italy (prescription restricted to hospital specialist), and 71% in Germany
Information from local Health Authorities

- High level of trust in information from non-profit organization
- Local website
  - HA or other organization
  - Information consistent with SPC and RMP
  - Alert by emails when breaking news available
  - Link to SPC, Q and A, Pharmacovigilance report form, Registry…
What is a realistic expectation/goal?

- The level of risk minimization needs to be consistent:
  - Unethical to have different minimization in one country vs. another*
  - Consistency is important from a legal perspective
  - Different tools can be used in different countries (adapted to local regulation, health practices and standard of care) with the same result
Challenge of Efficiency of Risk Minimization Activities

- Effective protection of patients vs. burden
- Feasibility and efficiency of some minimization tools: proportional answer to the risk and “preventability”
- Avoid too much and too busy communication tools for HCP!!!
- Effective measurement of the effectiveness of risk minimization activities
- Difficulties to measure the effectiveness of some minimization activities: e.g. rare outcomes
- Focus the communication/educational tools only on the concerning risk and not all risks: prioritization of risks based on their impact (individual and public health) and the potential of preventability
- Standardization of minimization tools and tools for measurement of effectiveness
Minimization methods beyond routine

- Communication - Education
  - Integration within other activities depending on stakeholders:
    - Health authorities: define an appropriate regulatory frame (delineating from promotional activities)
    - Health Care Prescribers: other educational activities, Continuous Medical Education (CME), standard medical practice
    - Patient: disease programs, several medications
    - Drug Company: marketing plans and market access strategy
  - Communication - Education tools includes non exhaustively
    - ‘Dear Healthcare Professional Letter’ (DHCP), most commonly used tool In EU & US
    - Training programs for prescribers (without certification)
    - Reminder tools (pocketsize cards)
    - Information in scientific journals or posted on websites
Conditions for minimization interventions

● Analysis of safety specifications leads to a risk management strategy (pharmacovigilance plan and need for risk minimization) to be endorsed by upper management.

● Only preventable risks can be minimized: two types of prevention
  • Avoid occurrence of Adverse Drug Reaction (ADR) by exclusion of at-risk patients
    • Risk factors need to have been identified
  • Stop the worsening course of a detected ADR. This requires evidence of:
    • Reversibility of the effect
    • A time course of the effect allowing window for intervention
      • Need to identify prognostic factors
    • Interest of biological markers of early detection of the effect
The science and statutory framework for pharmaceutical risk management continues to evolve.

FDA continues to learn more about various aspects of REMS, including
- making decisions about the need for REMS
- designing REMS programs that can be readily implemented and integrated into the existing healthcare system
- measuring REMS effectiveness
- minimizing the burden on patient access and the health care system.

Lessons learned highlight challenges and opportunities associated with REMS policy, standardization, integration and evaluation.
Unclear definitions make standardization difficult

Example: Patient/Prescriber Agreement and Enrollment Forms

<table>
<thead>
<tr>
<th>REMS</th>
<th>Form Name</th>
<th>Patient Agreement</th>
<th>Prescriber Agreement</th>
<th>Patient Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESAs</td>
<td>Patient and Healthcare Professional Acknowledgment Form</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Patient Information / Informed Consent</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Patient Enrollment Form</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lotronex</td>
<td>Patient Acknowledgment Form</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalomid</td>
<td>Patient-Physician Agreement Form</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

July 25, 2013 REMS Standardization and Evaluation Public Meeting
We are seeking feedback on specific REMS Tools

- **Prescriber-directed tools**
  - **Training**: What are the best ways to educate and train prescribers? (and other healthcare providers)
  - **Certification / Enrollment**: How can we streamline enrollment?

- **Patient-directed tools**
  - **Education**: What are the most effective and efficient ways to educate given the variety of information needs and learning styles?
  - **Counseling**: How can we improve patient counseling?
We are seeking feedback on specific REMS Tools

- Tools in dispensing settings:
  - Certification / Enrollment: How do we manage certification of dispensers, given the wide variety of dispensing settings in REMS?
  - Distribution controls: How can we make REMS compatible with established systems for procurement, distribution and dispensing?
A **Structured approach** (framework) is required, and **Five levels** proposed:

- **Level 1**: coverage and distribution, degree of implementation fidelity
- **Level 2**: Awareness
- **Level 3**: Risk knowledge/comprehension
- **Level 4**: Behavioural modification
- **Level 5**: Risk prevention/mitigation

The plan should be separately considered for all minimized risks.

The choice of measurement method is influenced by several factors:

- **Level and time course of risk**
- **Feasibility and costs**
- **Burden of the measurement method**

---

*CIOMS: Council for International Organizations for Medical Sciences is an international, non-governmental, non-profit organization established in 1949 by WHO and UNESCO (United Nations Educational, Scientific and Cultural Organization)*
CIOMS IX – Effectiveness of risk minimisation

Five-step model with examples of post-launch evaluation

LEVEL 5: Risk prevention/mitigation
- Pharmacoepidemiology to assess drug utilization in real life setting (e.g., PASS, DUS, Patient registry)
- Web-based interactive checklist
- Patient-reported outcomes

LEVEL 4: Behavioural modification
- Stakeholder surveys to assess knowledge & understanding
- Call centre feedback

LEVEL 3: Risk knowledge/comprehension
- Stakeholder surveys to assess knowledge & understanding
- Call centre feedback

LEVEL 2: RM tool awareness and usage
- Mailing house metrics
- Web download frequencies
- Stakeholder survey

LEVEL 1: RM tool distribution/coverage
- Mailing house metrics
- Web download frequencies
- Stakeholder survey

Increasing utility of information

Threshold(s) for determining success to be pre-defined
Conclusions

- Pharmacovigilance legislations are continuously evolving
- Risk management is an art and a science
- The format / template and content of the RMP differs across regions, but the ultimate goals remain the same
- Risk management is an opportunity to protect patients, avoid crises, and enhance our knowledge about our products
- Risk management plans need to be focused on products where risk activities beyond routine is necessary to ensure the safe use in patients (assessment and/or minimization)
- Risk management plans need to be focused on risks where minimization beyond routine may be possible (preventability) and potentially efficient!
- Approval of a RMP is just the beginning…!