Risk Management: An Industry Perspective
Pharmacovigilance Planning
Risk Minimization Measures
Safety Communication

Katharina Hartmann, PharmD
What does Safety imply?

In everyday terms:
Safety defined as exemption from injury or loss, freedom from danger, state of not being liable to danger or injury.


FDA Definition of Safety:
Safety means the relative freedom from harmful effect to persons affected directly or indirectly, by a product when prudently administered.

Harm: Physical or material injury; hurt; damage
What does Risk imply?

**In everyday terms:**
Risk as the chance of injury, damage, or loss. Therefore, to put oneself “at risk” means to participate either voluntarily or involuntarily in an activity or activities that could lead to injury, damage, or loss.


**In statistical and epidemiological terms:**
Risk is an expression of probability, usually (but not invariably) the probability of an adverse event, such as disease, injury, or death; i.e., risk can be quantified:

- Absolute risk: magnitude of the disease risk in a group of people with specific exposure
- Relative risk: strength of association between an exposure and a disease
- Attributable risk: proportion of disease risk that can be attributed to an exposure
Safety / Risk

Safety: Acceptance of risk - a personal / societal decision

Risk: Probability of occurrence of an adverse event for an individual within a specified time

Safety assessment is

assessment of the benefit / risk balance

EU Legislation: GVP Annex I Definitions Dec 2012:

Risk-Benefit Balance: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks [DIR 2001/83/EC Art 1(28a)], i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health [DIR 2001/83/EC Art 1(28)].
Safety: Balance of Benefit and Risk

**BENEFITS:**
- Prevention of disease
- Herd immunity
  ...
  ...

**RISKS:**
- Guillain Barre syndrome
- Encephalopathy
- ADEM (acute disseminated encephalomyelitis)
- Thrombocytopenia
- Vasculitis
  ...
  ...

Risk Profile: usually measured in clinical trials with one more of the following:
- Adverse Events / Determination of clinical signs and symptoms
- Physical examination (e.g., vital signs, neurological, ophthalmologic, general physical)
- Laboratory evaluations of biological samples (e.g. hematology, clinical chemistry, urinalysis)
- Special tests and procedures
- Psychiatric tests and evaluations
- Other test depending on the indication
Benefit – Risk Evaluation

Benefit – Risk evaluation is a continuous task during the whole lifespan of a medicinal product and should be presented

- in a structured manner
- with clear explanation of the methodology and reasoning used
- with clear assumptions, considerations and judgment or weighting that support the conclusions
Risk Management – old concept
Reactive Pharmacovigilance

Data collection → Signal detection → Signal verification → Risk assessment

Time

Regulatory actions
Risk communication

ADR known from pre- and postmarketing
Safety data from epidemiologic studies
ICH E2E Pharmacovigilance Planning - Risk Management

... the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit/risk balance.

“...shall comprise 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.”

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH Harmonised Tripartite Guideline
Pharmacovigilance Planning
E2E

Current Step 4 version dated 18 November 2004
Risk Management
ICH E2E Pharmacovigilance Planning

- The “**E2E: Pharmacovigilance Planning**” guideline is intended to aid industry and regulators in planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug.

- The guideline describes a method for documenting risks and proposes a structure for a pharmacovigilance plan.

- The guideline does not describe other methods to reduce risks from drugs, such as risk communication.

FDA and EMA adopted ICH E2E in 2005
Concept of the ICH E2E Guideline

Clinical Trials

Available Data/information

NDA

Review

Pharmacovigilance Specification
identified risks / potential risks missing information

Pharmacovigilance plan

Approval

Product Launch

On the Market

Pharmacovigilance Activities
Risk Management System

Risk Management is the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit/risk balance:

Guideline on Risk Management Systems for Medicinal Products for Human Use (EMA/CHMP/96268/2005)

EU Good Vigilance Practice, Module V: A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions (Annex V, ICH E2C(R2) Guideline).
Global Risk Management Planning
The Challenge of Reconciling the Differences

**FDA:** Risk assessment and risk minimization form what FDA calls *risk management*. **Risk Management** is an iterative process of

1. assessing a product’s benefit-risk balance,
2. developing and implementing tools to minimize its risks while preserving its benefits,
3. evaluating tool effectiveness and reassessing the benefit-risk balance,
4. making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance

**Risk Evaluation and Mitigation Strategies REMS**

**Europe:** A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

**GVP Module V and Module XVI**
# Risk Management in the EU

GVP Module V and GVP Module XVI

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### Guideline on good pharmacovigilance practices (GVP)

**Module V – Risk management systems (Rev 2)**

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<td>Draft Revision 2* finalised by the Agency in collaboration with Member States</td>
<td>16 February 2016</td>
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<td>23 February 2016</td>
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<td>24 February 2016</td>
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### Guideline on good pharmacovigilance practices (GVP)

**Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)**

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[Source](https://www.ema.europa.eu/en)
Risk Management – new concept
GVP Module V

From Risk Management to Benefit – Risk Management

Risk Management Cycle

Data Collection
monitor effectiveness and collect new data

Identify & Analyze
risk quantification and benefit assessment

Evaluate
benefit risk balance and opportunities to increase and/or characterize

Select & Plan
risk characterization / minimization and benefit maximization

Implement
risk minimization / characterization and benefit maximization

PASS / PAES

Clinical trials
Spontaneous reports
Literature
Epidemiological studies
Registries
……
Risk Management System (RMS)
Definition GVP Module V.B.1

‘a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions’. [DIR 1(28b)]
Principles of Risk Management
GVP Module V.B.2

• The overall aim of risk management is to ensure that the benefits exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole

• Single risk evaluation comprizes: risk identification, risk assessment, risk minimization and risk communication

• Multiple risk evaluation – risk management
  – Characterization of the safety profile including missing information
  – PV activities to further monitor the safety profile and adapt characterization
  – Risk minimizing measures and assessment of their effectiveness
Responsibilities for Risk Management within Industry

Marketing Authorization Holder / Applicant:

• Constantly monitoring product risks according to relevant legislation including reporting of the results to Competent Authority, as required

• Taking appropriate risk minimizing / benefit maximizing measures including active updates and prompt communication of new information; ensuring accuracy of this information

• Taking responsibility for the content and accuracy of the RMP by ensuring oversight by someone with appropriate scientific background

• Expectation:
  – RMP primarily considered a PV document
  – RMP to be managed by personnel with appropriate PV training (e.g., PV or RA Department)
Risk Management

Risk Management =
Risk Identification + Risk Assessment + Risk Minimization + Risk Communication

EU: In addition, Assessment of the impact of pharmacovigilance activities

Risk Management is a complex process which need governance structure.

Safety Management Teams (SMTs) are an operating model to ensure product safety and to document continuous and permanent safety evaluation of a medicinal product.
Risk Management Plan (RMP)

“a detailed description of the risk management system.” (DIR 2001/83/EC Art1 (28c))

- identify or characterise the safety profile of the medicinal product(s) concerned,
- indicate how to characterise further the safety profile
- document measures to prevent or minimise the risks associated
  - including assessment of effectiveness of the interventions
- document post-authorisation obligations that have been imposed as a condition of MA
- implicit requirements:
  - describe what is known about the safety profile
  - Indicate level of certainty that efficacy shown in clinical trials is seen in everyday practice
  - Include how effectiveness of risk minimisation measures will be assessed

Risks need to be understood in the context of benefit
Components of a Risk Management Plan

Risk Management Plan

Safety Specification
Summary of important identified risks, important potential risks and missing information (ICH E2E)

Pharmacovigilance Plan
Based on safety specification; Routine PV practices and action plan to investigate specific safety concerns (ICH E2E)

Risk Minimization
Activities to be taken to minimize the impact of specific safety concerns on the benefit-risk balance

Simmons, 2012
Global RMP – US / EU RMP Relationship

US RMP Relationship

1. Safety Specification
   ICH E2E

2. Pharmacovigilance Plan
   ICH E2E

3. Determine if risk minimization beyond label is warranted

4. Global Risk Minimization Strategy
   US Risk Minimization Activities
   (RiskMap = Risk Minimization Action Plan)
   REMS
   (Risk Evaluation & Mitigation Strategies)

EU RMP Relationship

1. Safety Specification
   ICH E2E

2. Pharmacovigilance Plan
   ICH E2E

3. Determine if risk minimization beyond label is warranted

4. Global Risk Minimization Strategy
   EU Risk Minimization Activities
Regional Variations of Global RMP

Safety Specification
ICH E2E

Pharmacovigilance Plan
ICH E2E

Determine if risk minimization beyond label is warranted

Global Risk Minimization Strategy

Regional Risk Minimization Activities

Regional Safety Specification Req

Regional PV Requirements
EU Risk Management Plan (RMP)
GVP Module V Template

Part I  Product Overview
Part II  Safety Specification
  Module SI: Epidemiology of the indications(s) and target populations(s)
  Module SII: Non-clinical part of the Safety Specification
  Module SIII: Clinical trial exposure
  Module SIV: Populations not studied in clinical trials
  Module SV: Post authorisation experience
  Module SVI: Identified and potential risks
  Module SVII: Additional EU requirements for Safety Specification
  Module SVIII: Summary of Safety Concerns

Part III  Pharmacovigilance Plan
Part IV  Plans for studies on effectiveness and long term efficacy
Part V  Risk Management Plan(s)
Part VI  Summary of Activities in the EU-BRMP
Part VII  Annexes
EU: Risk Management System – Vaccines

GVP P1

- GPV P1 supplements GVP Module V and presents vaccine-specific aspects of the Risk Management Plan (RMP) – in red vaccine-specific additions made in GPV P1:

  Part I  **Product Overview**
  Part II Safety Specification

  **Module SI**: Epidemiology of the indications(s) and target populations(s)
  **Module SII**: Non-clinical part of the safety specification
  Module SIII: Clinical trial exposure
  **Module SIV**: Populations not studied in clinical trials
  Module SV: Post authorisation experience
  **Module SVI**: Additional EU requirements for safety specification
  **Module SVII**: Identified and potential risks
  **Module SVIII**: Summary of safety concerns

  Part III  Pharmacovigilance Plan: **Routine PV activities, Additional PV activities**
  Part IV  **Plans for post-authorisation efficacy studies**
  Part V  **Risk minimisation measures**
  Part VI  Summary of activities in the risk management plan by medicinal product (EU-BRMP)
  Part VII  Annexes to the risk management plan
Stand-alone RMP summary
GVP Module V.B.12.1.

- Overview of disease epidemiology
- Summary of the existing efficacy data
- Summary of main safety concerns (identified, potential and missing information)
- Summary of risk minimization measures by safety concern (routine and additional)
- Planned post-authorization (safety and efficacy) development plan
- Studies, which are a condition of the marketing authorization
- Major changes to the RMP over time

Written in “lay language” and with links to Product Information
Risk Management Planning /1
Practical Considerations

When to start RM Planning – CIOMS VI* Principles

• Early in development; based on non clinical data & information on closely related compounds
• Establish a procedure & Multi Disciplinary Team (e.g., Safety Management Team SMT) and advisory bodies
• Determine background data
• Ready accessibility of all safety data
• Develop a proactive approach
• Establish time frames and milestones
• Decision making: focus on safety reviews

* Management of Safety Information from Clinical Trials 2005
Risk Management Planning

Practical Considerations

The Role of Epidemiology

- Important early in development and throughout the RM process
- Critical for the Safety Specification and PV Plan…..bridging the knowledge gap
  - Defines demographics & expected characteristics of the target population
    - co morbidities
    - anticipated AEFI profile in usual clinical practice
- Design of post marketing safety studies / registries
- Identification of existing databases
- Assess effectiveness of risk minimization measures
Practical Considerations

What format to use

- European template now in use since October 2006, new revised version 2 October 2018 - why reinvent the wheel?
- Aim for a globalized document; concept of a “Core RMP” based on ICH E2E and the European template with adaptation as required to meet local needs
- Getting the safety specification right is critical
- Use tabulations and graphical presentation of data
- Strategic risk minimization plan should be the same globally; implementation can be tailored to local medical practice
- Regulatory feedback and early discussion are useful to optimize content
Preparation of the RMP
Responsibilities

• The preparation is a highly collaborative exercise
• Project lead is within PV with roles and responsibilities of the different contributors / stakeholders clearly defined
• RMP preparation should be coordinated with preparation of other submissions
• The modular structure used to facilitate
  – Tailored modules per product and MAA type
  – Updates per module
  – Core RMPs and additional regional RMPs
  – Exchangeable modules with PSUR
Preparation of RMP: Regulatory guidance and structure

Core RMP follows EU requirements

- GVP (Good Pharmacovigilance Practice) Module V
- GVP P1: Product- or Population-Specific Considerations I: Vaccines

<table>
<thead>
<tr>
<th>Product overview</th>
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<tr>
<td>Safety specification</td>
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<tr>
<td>Plans for post-authorization efficacy studies</td>
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<tr>
<td>Risk minimization measures and evaluation of their efficacy</td>
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Modular Templates

GVP Module V

GVP P1 Vaccines
## Preparation of RMP: Cross-functional work sharing

Defines functions responsible for each section:

<table>
<thead>
<tr>
<th>Part</th>
<th>Description</th>
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<tr>
<td>Part I</td>
<td>Product(s) overview</td>
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<td>Part III</td>
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<td>Part IV</td>
<td>Plans for post-authorisation efficacy studies</td>
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<tr>
<td>Part V</td>
<td>Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)</td>
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<tr>
<td>Part VI</td>
<td>Summary of the risk management plan</td>
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<tr>
<td>Part VII</td>
<td>Annexes</td>
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</tbody>
</table>
Preparation of RMP

**Analyze safety data using updated analysis plan**

**Develop safety specification**

**Develop pharmaco-vigilance plan**

**Define types of post-launch risk minimization interventions**

**Arbitration/Approval**

**Yes**

**Draft Risk Management Document**

**Approvable?**

**Yes**

**Marketing Application**

**No**

**Revise RMP as appropriate**

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**GPS responsible for safety data**

**PT and ABT Medical responsible for efficacy data**

**Statistical support needed for both safety and efficacy analyses**

**GPS responsible for quantitative risk benefit analyses (when methodology available)**

**PT and ABT Medical assess qualitative benefit/risk value; Marketing provides market value**

**GPS, ABT(s) and PT collaborate, GPS assures public health perspective**

**GPLC advises on RMP**

**Individual functions develop detailed interventions**

**GSIC owns template and manages RMP document**

**GPS VP, PT or Affiliate Medical Director sign off on final RMP(s). EU QP sign off on EMEA RMP.**

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**Planning for final document preparation is coordinated with other submission documents.**

**GPS, ABT(s) and PT collaborate, GPS assures public health perspective**

**GPLC advises on RMP**

**Individual functions develop detailed interventions**

**GSIC owns template and manages RMP document**

**GPS VP, PT or Affiliate Medical Director sign off on final RMP(s). EU QP sign off on EMEA RMP.**
When to submit a RMP

• For all new marketing applications RMP describing the RMS for the medicinal product concerned, together with summary
• At any time during a product’s life-cycle, i.e., during pre- and post-licensure phases
• Significant change in existing marketing authorization:
  – New dosage form
  – New route of administration
  – New manufacturing process of a biotechnologically-derived product
  – Pediatric indication
  – Other significant change in indication (e.g., new target population, a.o.)
• At request of Regulatory Authority when a concern about a risk affecting the Benefit / Risk balance
• At the time of renewal (if the product has an RMP)
Updates to the RMP

- If an RMP has previously been submitted, any following submissions must be in the form of an update.
- Each RMPs must have distinct version number / date.
- Clean and track-change RMP versions to be submitted.
- Cover letter, detailing the changes since the last submitted version.
- Submission of RMPs in general aligned with PSUR submissions.
- If no changes since previous RMP submission MAH may submit a letter explaining that there is no change and not submit an RMP.
- If requirement for providing routine RMP updates is not specified as part of MA routine RMPs to be provided:
  - annually until the first renewal of the MA
  - every three years thereafter.

Ensure if National Authority accepts RMPs based on GVP with country-specific information in the cover letter.
<table>
<thead>
<tr>
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<tr>
<td>Part I Product(s) overview</td>
<td>Module 2.3 Quality overall summary</td>
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<td>Module 4 Non-clinical study reports</td>
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<td>PSUR section</td>
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### RMP versus PSUR
The two primary post-authorization PV documents

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<th>PSUR / PBRER</th>
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<td><strong>Main focus:</strong></td>
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<tr>
<td>Pre- and postauthorisation risk-benefit management and planning</td>
<td>Integrated post-authorisation risk-benefit assessment</td>
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<td>Risk minimisation plan</td>
<td>Ensuring benefit-risk balance remains favourable</td>
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<td>PASS / PAES: data collection</td>
<td>Signal detection and evaluation</td>
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<td>Risk minimisation measures</td>
<td>Establishing and documenting the “core safety profile“</td>
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<tr>
<td>Ensuring effectiveness of measures</td>
<td>Ensuring up-to-date product information</td>
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Tools to be used differently, depending upon where the product is in its life-cycle.
Challenges and complexities

...include but are not limited to:

Local requirements differ

Resource conflicts with other submission / launch activities

Coordination/consistency with CTD / PSUR

Health Authority Requests need to be implemented

PV System to be established

Budget
Important risks

An important risk?

Clearly an important risk!

Most discrepancies in understanding important risks are related to disability, life-threatening conditions or medical significance – as these assessments require medical judgement.
**Important identified / potential risks**

Identified / potential risks:

- negative impact on the benefit – risk balance
- implications for public health
- depends on several factors:
  - impact on the individual patient
  - seriousness of the risk
  - frequency
  - preventability

In general:

any risk that is likely to be included in the contraindications / warnings and precaution section of the product information
Identified risk:
- Occurrence with an adequate evidence of an association with the vaccine.
  
  Examples:
  - Demonstrated in preclinical safety problems and observed in clinical trials
  - AEFI's from clinical or epidemiological studies suggesting a causal relationship
  - AEFI's suggested by a number of well-documented spontaneous reports with causality strongly supported by temporal relationship and biological plausibility

Potential risk:
- An untoward occurrence with suspicion of an association between the vaccine and the AEFI, the association, however, not confirmed.
  
  Examples:
  - Preclinical safety problems, not observed in clinical trials
  - AEs from clinical or epidemiological studies, of which the risk parameters are suspicious for a safety problem
  - AEFIs known from other vaccines with the same indication
  - AEs to be expected based on the pharmacological action of the drug
Important identified risks for DTPw-HBV

Example

CIOMS Guide to Vaccine Safety Communication 2018

Example 3.2.3: The introduction of pentavalent vaccines in Kerala, India, supported by close interactions with the healthcare community and the media

A quadrivalent combined bacterial and viral vaccine protecting against diphtheria, tetanus, pertussis and hepatitis B, and was assessed by the European Medicines Agency (EMA) in collaboration with WHO, in order to facilitate its use in countries outside the European Union (EU). Based on the clinical trials, the following was classified as ‘important identified risks’: allergic reactions, high fever, convulsions, hypotonic-hyporesponsive episodes; and the following as ‘important potential risks’: apnoea in prematurely born children, fainting, brain disorder. In addition, the lack of safety and immunogenicity in children born prematurely was classified as ‘missing information’. Given these safety specifications, no risk minimization measures other than the product information were considered necessary. Information on the identified and potential risks, including warnings and precautions for use to minimize their occurrence and severity of impact, has been included in the package leaflets for carers and the healthcare professional information.
Risk Minimization Plan

When is a specific Risk Minimization Plan needed?

- Not invariably but requires justification in the EU (approx. 18% of RMPs)
- Additional measures to mitigate known risks need to be:
  - Appropriate to the level of risk
  - Feasible in practice
  - Effectively communicated
  - Principles set at a global level but implementation according to local regulations/medical culture etc
  - Multi functional input and close coordination with affiliates important

- Current toolkit is limited
  - Need to be able to provide example(s) of proposed tools etc
  - Need to propose how effectiveness will be monitored; impact on spontaneous reporting unlikely to be acceptable
Risk Minimisation Measures (RMM) Methods

• Information:
  • Product information for healthcare professionals (in the EU the SmPC)
  • Package leaflet (Patient Information Leaflet PIL)
  • Labelling on outer packaging
  • Training
  • Checklists
  • Educational material
  • Dear Healthcare professional communication (DHCP)
  • Pregnancy prevention program

• Prescribing restrictions (legal status):
  • In-patient use only
  • Specialised physicians only
  • Special administration
  • Controlled distribution systems

  Rather drug specific:
  Restrictions in quantity (e.g., doses / package unit)
  Surveillance of the patients
  • Registries
  • Named patient use
  • Restricted access programs
  •...
Risk Minimization Measures (RMM)

Evaluation of effectiveness

Evaluating the effectiveness of RMM by means of a dual-evidence approach*

*Pietro et al 2012
Guideline on good pharmacovigilance practices (GVP)
Module XV – Safety communication (Rev 1)

Date for coming into effect of first version
Draft Revision 1 finalised by the Agency in collaboration with Member States
Draft Revision 1 agreed by the European Risk Management Facilitation Group (ERM F G)
Draft Revision 1 adopted by Executive Director
Release for consultation
End of consultation (deadline for comments)
Revised draft Revision 1 finalised by the Agency in collaboration with Member States
Revised draft Revision 1 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)
Revised draft Revision 1 adopted by Executive Director as final
Date for coming into effect of Revision 1*
GVP Module XV Safety communication
Principles

• Provide timely and evidence-based information on the safe use of vaccines
• Deliver relevant, clear, accurate and consistent messages for the right audience at the right time
• Tailor to the appropriate audience by using appropriate language, respecting the different levels of knowledge and maintaining accuracy and consistency of the information
• Consider safety information communication throughout the PV and RM process as part of risk assessment and risk minimization measures
• Adequate coordination and cooperation between the different parties (e.g., Authorities, public bodies, MAH etc.)
• Present the risk in context of the benefits
• Address the uncertainties related to the safety concern
• Include risk on non-treatment as compared to risk of treatment
• Evaluate the effectiveness of safety communication, if possible
Safety communication – Vaccines

GVP PI

• Vaccine specific safety communication must
  – include information on avoiding errors in vaccine handling, administration and reiterating precautions and warnings
  – describe the benefits of vaccines
  – explain the risks for individuals and the population of a decrease in vaccination coverage
  – consider that risk perception may differ between stakeholders, esp. in case of uncertainty of a causal association
  – contain relevant background rates and exposure data when quantifying safety concerns.

• Communication planning must include preparedness for frequent public communication needs (e.g., on excipients, residues, identified or potential risks, coincidental events, temporal versus causal association, etc.).

• Regulatory Authorities must
  – ensure appropriate communication with public and media
  – maintain a high level of transparency on how regulatory decisions were reached.
Risk communication

- Black box warning
- Direct Healthcare Professional Communication (DHPC) letter (“Dear Doctor Letter”)
- Change of product labeling
- Publications
- Training
- Seminars
- ...
1. Situation and Monitoring
   - Vaccine Safety
   - Epidemiology
   - Public
     - Monitoring of the public KAP, concerns, rumors and information needs

2. Communication objectives

3. Strategic design of the communication intervention
   - Target audiences
   - Change model
   - Key messages
   - Communication tools and dissemination mechanisms in a mixed media approach
   - Interactions with journalists and community advocated / activists
   - Timetable
   - Transparency provisions

4. Monitoring and evaluation
Risk Management Plans
Industry Experience

- Increasing trend to request EU specific RMP vs global document
  - e.g., wish to see specific reference to SPC sections vs generic statements relating to the CCSI
- Strong emphasis on paediatric use
  - May require a paediatric RMP
- Requests for:
  - studies in individual countries based on theoretical concerns
  - country specific PV activities / local RMPs where an EU RMP has been agreed
  - country specific utilization studies
  - Variable interpretation of what constitutes an important risk........
Risk Management

“And now at this point in the meeting I’d like to shift the blame away from me and onto someone else.”