Module 9: Risk Management

Contents

1. Introduction to Risk Management

The decision to give a marketing authorization to a drug is based on that its benefits outweighs the risks under conditions specified in the product labelling (i.e. benefits for therapeutic indication (s) mentioned, and the product is to be used as per the instructions and recommendations in product label). This decision is based on the information available at the time of approval [1]. At the time of product authorisation, information on the safety of a medicinal product is relatively limited [due to limitations of clinical development of the medicinal product: relatively small numbers of patients included in clinical trials; restricted population included in terms of age, gender and ethnicity; restricted co-morbidity (due to specified inclusion criteria); relatively short duration of treatment etc.] [2].

A medicinal product will have multiple risks associated with its use and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, due to above-mentioned limitations of clinical development of the medicinal product, not all risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post authorisation/post marketing period i.e. the knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed [1,2].

2. Definitions

Below are important terms with their definitions in context of risk management:

- **Harm**: Physical injury and/or damage to health.
- **Hazard**: A potential source of harm.
- **Risk**: The probable rate of occurrence of a hazard causing harm and the degree of severity of the harm.
- **Residual risk**: Risk remaining after risk control measures has been taken.
- **Risk Analysis**: The investigation of available information to identify hazards and to estimate risks.
- **Risk assessment**: Overall process comprising a risk analysis and a risk evaluation.
- **Risk control**: Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels.
- **Risk estimation**: Process used to assign values to the probability of occurrence of harm and the severity of that harm.
- **Risk evaluation**: Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk
- **Safety**: Freedom from unacceptable risk of harm.
- **Severity**: Measure of the possible consequences of a hazard.
- **Signal**: The Report of the Council for International Organizations of Medical Sciences (CIOMS) Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) defines a signal as information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [3].

3. Signals and Risks

A Signal, life of a signal and Risks (risk detection, impact analysis and characterization of a risk)

As per the GVP module IX (dated February 2012) [3], if a signal is detected (either from internal routine signal detection activities/based on a Health Authority (HA) request/from data analysis in aggregate safety reports or by frequency analysis (ex. Empirica), it would be analyzed further for its validation*.

* Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis [3].

Validated signals will be analyzed and evaluated for impact analysis (which include causal association, strength of evidence of association of the signal with drug treatment, impact on individual patient health, impact on public health, its preventability, reversibility, potential mechanism of action if any etc.) to assess whether it is a identified risk or potential risk.

As per the Good Pharmacovigilance (PVP) Guidelines Module V (Rev 2, dated February 2016) [2],

An **identified risk** *is*

*"**An undesirable outcome** for which there is **sufficient scientific evidence** that it is caused by the medicinal product.*

In a clinical trial, the comparator may be placebo, active substance or non-exposure. Where an adverse event which is an identified risk for a comparator occurs at a similar (active comparator) or higher frequency with a new product, this suggests that the adverse event should also be an identified risk for the new product."

<u>The definition has been changed recently. Definition of an identified risk (as per GVP module V, Rev I (dated April 2014)</u> [4] ***<u>was</u>***

*"An **untoward occurrence** for which there is **adequate evidence** of an association with the medicinal product of interest.*
Examples include:

- *An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;*
- *An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;*
- *An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.*

In a clinical trial, the comparator may be placebo, active substance or non-exposure".

Potential risk:
As per the GVP module V (Rev 2) [2], a potential risk is:

*"An **undesirable outcome** for which there is a **scientific basis for supposition of a causal relation** with the medicinal product (e.g. a signal, a class effect plausible also for the new product, findings from (non-) clinical studies) but where **there is insufficient support to conclude that there is a causal association**."*

As per the GVP Module V (Rev 1) [4]*, A potential risk was*
*"An **untoward occurrence** for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.*
Examples include:

- *Toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;*

- *Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship;*
- *A signal arising from a spontaneous adverse reaction reporting system;*
- *An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product."*

Missing information

As per GVP module V (Rev 2), missing information is [2]:

"Gaps in knowledge about a medicinal product, related to the anticipated utilisation patterns such as long-term use or use in particular patient populations, which could be clinically significant. For instance:

- Safety profile with long-term use when there are suspected potential risks related to cumulative or long-term exposure;
- Use is anticipated in populations not studied (e.g. pregnant women or patients with severe renal impairment) and the safety profile is expected to be different in these populations;
- Off-label use is likely; if a markedly different safety profile than that in the target population is suspected, the specific safety concern that might be associated with off-label use should be specified rather than the global term 'off label use'."

As per GVP module V (Rev 1), missing information is [3]

"Gap in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant. For example, due to exclusion criteria of clinical trial, a medicinal product's safety and efficacy were not evaluated in children, elderly patients and pregnancy and lactating women, hence, there is a gap in knowledge of safety and efficacy of the medicinal product in these populations groups, therefore, these populations would be considered as special populations for the medicinal product and safety/efficacy in these populations would be missing information.

Based on the impact analysis and characterization of the risk, a risk could be categorized as important or not important.

As per the GVP guidelines (Module 5, rev 2) [2],

"*An important identified or potential risk is a risk that could have an impact on the benefit-risk balance of the product when further characterised and/or if not managed appropriately in daily clinical practice, and which therefore would usually lead to further evaluation as part of the pharmacovigilance plan within the RMP (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use; which populations are particularly at risk) or will require risk minimisation activities beyond routine risk communication.*

A potential risk will not be considered 'important' if it has minimal impact on patients or, upon further characterisation, does not require at least routine risk minimisation activities that are intended to affect clinical practice, even if a strong causal relationship were found. For example, if a potential risk, once confirmed, requires dose reduction or more frequent monitoring in certain populations, then that would qualify the potential risk as 'important'. If confirmation of the potential risk as an identified risk would not result in any changes of the monitoring requirements, then such a potential risk would not usually be considered 'important'. Where there is a justified supposition that an adverse reaction might be associated with the long-term use, off-label use, or use in populations not studied (e.g. because similar effects have been seen with other products of the same class), the adverse reaction should be considered a potential risk, and if deemed important, should be included in the RMP as an important potential risk."

As per GVP module V (Rev 1) [4]*,*

"What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.**"**

Safety concerns are important identified risks, important potential risks and missing information [1].

Risk: The probable rate of occurrence of a hazard causing harm and the degree of severity of the harm. Risk is a broad concept and applies to everything in life. We take risks when we drive a car, go to work, eat a meal, and take a drug.

Risk can be defined in many ways [1]:

- Exposure to a possibility of loss or damage.
- The quantitative or qualitative possibility of loss that considers both the probability that something will cause harm and the consequences of that something.
- The probability of an adverse event's resulting from the use of a drug in the dose and manner prescribed or labeled, or from its use at a different dose or manner or in a patient or population for which the drug is not approved.
- The exposure to loss of money as a result of changes in business conditions, the economy, the stock and bond markets, interest rates, foreign currency exchange rates, inflation, natural disasters, and war.

Risk Management System [2] is 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 activities and interventions [DIR Art 1(28b)].

Risk Management Plan (RMP) [2] is a detailed description of the risk management system [DIR Art 1(28c)].

Risk Minimization Activity [2]: An intervention intended to prevent or reduce the occurrence of an adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur.

Objective of risk management [2]: The aim of risk management is to ensure that the benefits of a medicinal product outweigh the risks.

In the European Union (EU), as well as complying with the legislation, the primary document and process for risk management adheres to the principles in the International Conference for Harmonisation (ICH) Guideline E2E on Pharmacovigilance Planning.

References:

1. ICH Harmonized Tripartite Guideline on Pharmacovigilance Planning E2E (Current Version Step 4, dated November 2004). Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf [Last accessed on May 2019].
2. European Medicines Agency's Guidelines on Good Pharmacovigilance Practice Module V-Risk Management System (Revision 2, dated 24 February 2016). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500202424.pdf [Last accessed on May 2019].
3. European Medicines Agency's Guidelines on Good Pharmacovigilance Practice Module IX –Signal management (dated 20 February 2012). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123209.pdf [last accessed on May 2019].
4. European Medicines Agency's Guidelines on Good Pharmacovigilance Practice Module V-Risk Management System (Revision 1, dated 15 April 2014). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf [Last accessed on May 2019].

4. Regulatory Requirement of Risk Management

The United State (US) Food and Drug Administration (FDA) first published a document on its thinking in May 1999, entitled "Managing the Risks from Medical Product Use and Creating a Risk Management Framework." It addressed pre- and post-marketing risk management and the FDA's role. Further publications have extended and elaborated the FDA's position. The FDA has published three guidances for industry on risk management [1]:

- ✓ Premarketing Risk Assessment
- ✓ Development and Use of Risk Minimization Action Plans (RiskMAPs)
- ✓ Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

The first guidance, on premarketing risk assessment, focuses on measures companies might consider throughout all stages of clinical development of products.

The second guidance, on RiskMAPs, describes how industry can address specific risk-related goals and objectives. This guidance also suggests various tools to minimize the risks of drug and biologic products. This guidance has been superseded by a later FDA guidance on REMS.

The third guidance, on the post-marketing period, identifies recommended reporting and analytical practices to monitor the safety concerns and risks of medical products in general use.

In September 2007, with the passage of the Food and Drug Administration Amendments Act (FDAAA), the concept of the RiskMAP was superseded by the new REMS [1].

In September 2009, the FDA issued a major guidance entitled "Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications".

European Union (EU) Risk Management Plans (RMPs)

The fundamental documents establishing pharmacovigilance (PV) and RMP concepts for the EU are Directive 2001/83/EC and Volume 9A. A guideline was published by the EMEA in 2005 and was based to a large degree on ICH E2E. It has since been incorporated in Volume 9A [1].

When a RMP is needed:

At any point in a drug's life cycle, an RMP may be needed. The health authority (HA) and/or the Marketing Authorization (MA) applicant may determine an RMP is needed [1,2]

- ✓ At the time of application for a new MA or a new active substance
- ✓ For "a similar biological medicinal product"
- ✓ For certain generic/hybrid products
- ✓ For an application for pediatric use
- ✓ For a significant change in marketing: new dosage form, new route of administration, new manufac turing process of a biotech product, significant new indication, new pediatric indication
- ✓ For certain other situations, including fixed combination products

References:

1. Risk: What is it? Risk management and Assessment, Risk Evaluation and Mitigation Strategy, Risk Management Plan. Cobert's Manual of Drug Safety and Pharmacovigilance. In: Cobert B. 2nd Edition. Jones and Bartlett Learning, LLC, 2012; Sudberry, MA. p: 186-197.
2. Risk management Plan. Available from; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp [Last accessed on May 2019].

5. ICH E2E

ICH E2E Guideline was finalized in 2004 and is intended to aid in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug. The main focus of this guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of the application for marketing [1].

Background and Scope:

The guidance is proposed for new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnology-derived product) and for established products to be introduced to new populations or for new indications, or where a new major safety concern has arisen [1].

A safety specification and pharmacovigilance plan can also be developed for products already on the market (e.g., new indication or major new safety concern). The plan could be used as the basis for discussing pharmacovigilance activities with regulators in the different ICH regions and beyond.

For products with important identified risks, important potential risks, or important missing information, the pharmacovigilance plan should include additional actions designed to address these concerns. For products for which no special concerns have arisen, routine pharmacovigilance should be sufficient for post approval safety monitoring, without the need for additional actions (e.g., safety studies).

During the course of implementing the various components of the plan, any important emerging benefit or risk information should be discussed and used to revise the plan.

As mentioned above, ICH E2E guideline describes a method for summarising the safety concerns (safety concerns: important identified risks, important potential risks, and important missing information), including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and

conduct of observational studies. It does not describe other methods to reduce risks from drugs, such as risk communication. The guideline takes into consideration ongoing work in the three regions and beyond on these issues. This guideline does not cover the entire scope of pharmacovigilance [1].

The guideline is divided into the following sections [1]:

- Safety Specification;
- Pharmacovigilance Plan;
- Annex – Pharmacovigilance Methods.

Safety Specification

The Safety Specification is a summary of the safety concerns (i.e. important identified risks of a drug, important potential risks, and important missing information). It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period [1].

Elements of the Specification [1]:

The format and contents of safety specification should focus on the identified risks, important potential risks, and important missing information. It should refer to the three safety sections in the Common Technical Document (CTD). The following elements should be considered for inclusion:

- Non-Clinical
- Clinical
- Identified risks that require further evaluation
- Potential risks that require further evaluation
- Epidemiology
- Pharmacology class effects

Non-Clinical [2]: This section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT/QTc interval prolongation; nervous system; etc.);
- Drug interactions;
- Other toxicity-related information or data. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

Clinical [1]**:** This section should present

- Limitation of the human safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria, populations not studied in clinical development and implication of such limitations in context to predicting the safety of the product in the marketplace); Populations to be considered should include (but might not be limited to): Children/ elderly/ pregnant or lactating women/ patients with relevant co-morbidity such as hepatic or renal impairment/patients with disease severity different from that studied in clinical trials/ sub-populations carrying known and relevant genetic polymorphism/ patients of different racial and/or ethnic origins. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice [1].
- The worldwide experience should be briefly discussed, including the extent of the worldwide exposure, any new or different safety issues identified, any regulatory actions related to safety, and populations not studied in the preapproval phase [1].
- Adverse Events (AEs) / Adverse Drug Reactions (ADRs) [the important identified and potential risks that require further characterisation or evaluation; discussion of risk factors and potential mechanisms that apply to identified] [1].

Identified risks that require further evaluation: More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.). Potential risks that require further evaluation Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association [1].

Potential Risks that require further evaluation:

- Important potential risks should be described and the evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterize the association.
- Identified and potential interactions, including food–drug and drug–drug interactions should be discussed with consideration of the evidence, and potential health risks posed for the different indications and in the different populations should be discussed. In this subsection, identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

Epidemiology [1]

- The epidemiology of the indication(s) should be discussed including incidence, prevalence, mortality and relevant co morbidity and should take into account whenever possible stratification by age, sex, and racial or ethnic origin. Differences in the epidemiology in different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.
- For important AEs that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates).

Pharmacological Class Effects [1]: The Safety Specification should identify risks believed to be common to the pharmacological class.

Summary [1]

At the end of the Safety Specification a summary should be provided of the:

Important identified risks; important potential risks; important missing information.

Pharmacovigilance Plan [1, 2]

The pharmacovigilance plan should be based on the safety specification and developed by the sponsor. It can be discussed with regulators during product development, before approval of a new product (i.e., when the marketing application is submitted), or when a safety concern arises post-marketing. It can be a stand-alone document.

For products for which no special concerns have arisen, routine pharmacovigilance should be sufficient for post approval safety monitoring, without the need for additional actions (e.g., safety studies). However, for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

It should be updated as important information on safety becomes available and milestones are reached.

The format and content should include the following:

- Summary of ongoing safety issues, including the important identified risks, potential risks, and missing information.
- Routine pharmacovigilance practice should be conducted for all medicinal products, regardless of whether additional actions are appropriate as part of a pharmacovigilance plan. This routine pharmacovigilance should include the following:
    - Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner.
    - The preparation of reports for regulatory authorities, including expedited ADR reports and PSURs.
    - Continuous monitoring of the safety profile, including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities.
    - Other requirements, as defined by local regulations.
    - Action plan for safety issues:
        - The plan for each important safety issue should be presented and justified according to the safety issue, objective of proposed action,

action proposed, rationale for proposed action, monitoring by the sponsor for safety issue and proposed action, and milestones for evaluation and reporting. Any protocols for specific studies may also be provided.

- Summary of actions to be completed, including milestones:
    - An overall pharmacovigilance plan for the product, bringing together the actions for all individual safety issues, should be presented and organized in terms of the actions to be undertaken and their milestones.
    - It is recommended that milestones for completing studies and for submitting safety results be included in the pharmacovigilance plan. The milestones should reflect when exposure to the product will have reached a level sufficient to allow potential identification/characterization of the AEs/ADRs of concern or resolution of a particular concern and when the results of ongoing or proposed safety studies are expected to be available.
    - These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment, and license renewals) and used to revise the pharmacovigilance plan.
- Pharmacovigilance methods
        - The best method to address a specific situation can vary, depending on the product, the indication, the population treated, and the issue to be addressed. When choosing a method to address a safety concern, sponsors should use the most appropriate design.
        - Design and conduct of observational studies
        - Carefully designed and conducted pharmacoepidemiologic studies, specifically observational (noninterventional, nonexperimental) studies, are important tools in pharmacovigilance.
        - A protocol should be finalized and experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists, and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. A study report after completion, and interim reports if

appropriate, should be submitted to the authorities according to the milestones within the pharmacovigilance plan.

- The sponsor should follow good epidemiologic practice for observational studies and internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.

- Annex
  - A detailed discussion of pharmacovigilance methods is appended to the document to which the reader is referred for further details.

6. Risk Management Plan (RMP)

A RMP includes: a medicine's safety profile; information on how the risk associated with drug treatment will be prevented or minimized in patients (i.e. risk minimization activities); plans for further studies and other activities to gain more knowledge regarding safety and efficacy of the medicine [Post authorization efficacy studies (PAES)/Post authorization safety studies (PASS)]; measuring the effectiveness of risk minimization measures, need of additional risk minimization activities (if applicable). [1]

The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a medicinal product's life cycle. The RMP is a dynamic document that should be updated throughout the life cycle of the product(s). [1]

As per the GVP module V (Rev 2, dated February 2016) [1], the RMP contains the following:

a). Identification or characterisation of the safety profile of the medicinal product including what is known and not known and, importantly, which risks need to be further characterised or managed proactively (the 'safety specification');

b). Planning of pharmacovigilance activities to characterise and quantify serious or clinically relevant risks of adverse reactions, and to identify new adverse reactions (the 'pharmacovigilance plan');

c). Planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

Format and content of a RMP

As per GVP Module V, RMP has seven parts [1]:

- **Part I** (**Product Overview**):
- **Part II (Safety Specification):** This part is subdivided in eight modules.
    - **Module SI (**Epidemiology of the indication(s) and target population): This RMP module should include incidence, prevalence, outcome of the target disease (i.e. indications) and relevant co-morbidity, and should when relevant for assessment of safety and risk management be stratified by age, gender, and racial and/or ethnic origin. Risk factors for the disease and the main existing treatment options should also be described. The emphasis should be on the epidemiology of the proposed indication in the EU.
    - **Module SII (**Non-clinical part of the safety specification): This RMP module should present a high-level summary of the important non-clinical safety findings, for example:
        - Toxicity (key issues identified from acute or repeat-dose toxicity, reproductive/developmental toxicity, genotoxicity, carcinogenicity);
        - Safety pharmacology (e.g. cardiovascular system, including QT interval prolongation, nervous system);
        - Other toxicity-related information or data.
    - **Module S III (**Clinical trial exposure): In this module, summary information on the patients studied in clinical trials should be provided in an appropriate format (e.g. tables/graphs). The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time exposed to the medicinal product.
    - **Module S IV (**Populations not studied in clinical trials): In this module, populations that are considered under missing information should be described.
    - **Module SV (**Post-authorization experience): If post-marketing data are available from an authorized product from the same MAH containing the same active substance or from post-authorization experience in other regions outside EU, where the product is already authorized, the data should be

discussed in this RMP module. It should only provide an overview of experience in the post-authorization phase that is helpful for risk management planning purposes.

- **Module SVI (**Additional EU requirements for the safety specification): Some safety topics were not included in the ICH-E2E format, but are thought to be of particular interest due to either EU legislation or prior experience of a safety issue. This includes:
  - The potential for misuse for illegal purposes, and, where appropriate, the proposed means of limiting this; e.g. limited pack size, controlled distribution, special medical prescription
- **Module S VII (**Identified and potential risks): This module should provide a focused discussion on the identification of important identified and important potential risks, and missing information (i.e. safety concerns). Safety topics derived from specific situations/data sources are thought to be of particular interest to be discussed in module SVII, as appropriate:
  - Potential harm from overdose, whether intentional or accidental
  - Potential for risks resulting from medication errors, defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design.
  - Potential for transmission of infectious agents
  - Potential for off-label use
  - If a risk common to other members of the pharmacological class is not thought to be an important identified or important potential risk with the concerned medicinal product, the evidence to support this should be provided and discussed
  - Risks related to identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to the

treatments for the condition, but also in relation to commonly used medications in the target population

- Risks in pregnant and lactating women
- Effect on fertility – appropriate risk minimization measures should be considered.

- This module should contain the initial identification of safety concerns and is expected to be populated for RMPs submitted with the initial marketing authorization (MA) application, or with a new RMP submitted post-authorization (at the competent authority's request or without request).
  - In this section, for each risk, the following information should be summarized and discussed:
    - For risks considered as safety concerns], the level of scientific evidence of an association (including when relevant a causality assessment);
    - Seriousness;
    - Frequency;
    - Clinical and benefit-risk impact;
    - For risks not taken forward as safety concerns] the justification for not including them as a safety concern.

Guidelines for presentation of important identified and important potential risks data [1]:

- Name of the risk (using MedDRA terms when appropriate);
- Frequency (e.g. incidence rates with confidence intervals);
- Potential mechanism; Evidence source(s) and strength of the evidence (i.e. the scientific basis for suspecting the association);
- Impact on the individual patient (e.g. absolute risk, relative risk, severity, reversibility, and long- term outcomes, as well as quality of life);
- Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors);
- Preventability (i.e. predictability of a risk; whether risk factors have been identified that can be minimized by routine or additional risk minimization activities other than

general awareness using the PI (Product information); possibility of detection at an early stage which could mitigate seriousness);

- Impact on the benefit-risk balance of the product;
- Public health impact (e.g. absolute risk in relation to the size of the target population and consequently actual number of individuals affected, or overall outcome at population level).

Guidelines for presentation of missing information data [1]**:**

- Name of the missing information (using MedDRA terms when appropriate);
- Description of the risk anticipated in the population not studied, or the description of a population in need of further characterization;
- Evidence that the safety profile is expected to be different than in the general target population;
- The changes in the benefit-risk balance that are anticipated if a causal relation between a further characterized risk and the product is confirmed to be strong (i.e. worst-case scenario).
    - **Module S VIII (**Summary of the safety concerns): In this section, a list of safety concerns should be provided with the following categories: important identified risks; important potential risks; missing information.

Part III: **Pharmacovigilance Plan (including post authorization safety studies)**

PvP plan provides a structured plan for:

- The investigation of whether a potential risk is real or not;
- Further characterization of safety concerns including severity, frequency, and risk factors;
- How missing information will be sought;
- Measuring the effectiveness of risk minimization measures.

It does NOT include actions intended to reduce, prevent or mitigate risks; these are discussed in RMP part V.

The pharmacovigilance plan should focus on the safety concerns summarised in RMP module SVIII of the safety specifications and should be proportionate to the benefits and risks of the product.

Pharmacovigilance activities can be divided into routine and additional pharmacovigilance activities.

Part IV: Plans for post-authorization efficacy studies (PAES)

This RMP part should include a list of post-authorisation efficacy studies (PAES) imposed as conditions of the marketing authorisation or when included as specific obligations in the context of a conditional MA or a MA under exceptional circumstances.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimisation activities)

This part should provide details of the risk minimisation measures which will be taken to reduce the risks associated with respective safety concerns.

Risk minimization activities might be routine or additional.

Routine risk minimization activities: Routine risk minimisation activities are those which apply to every medicinal product. These relate to: the summary of product characteristics, the labelling, the package leaflet, the pack size, the legal status of product.

Additional risk minimization activities: Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product.

Part VI: Summary of activities in the risk management plan by product

In this part, a summary of the RMP for each authorised medicinal product shall be made publicly available and shall include the key elements of the RMP.

Part VII: Annexes

Annex 1: Annex 1 is the structured electronic representation of the EU RMP.

Annex 2: Annex 2 should include a tabulation of studies included in the pharmacovigilance plan

Annex 3: Protocols for proposed, on-going, and completed 1028 studies in the pharmacovigilance plan

Annex 4: Specific adverse event follow-up forms

Annex 5: Protocols for proposed and on-going studies in RMP part IV

Annex 6: Details of proposed additional risk minimisation activities

Annex 7: Other supporting data (including referenced material)

As per the GVP module V (Rev 2) [1], in the life cycle of the products the list of safety concerns in the RMP will be reduced:

- *It may be that **important potential risks can be removed from the safety specification in the RMP** (e.g. when accumulating scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important, or when there is no reasonable expectation that any pharmacovigilance activity can further 26inimization the risk, thus questioning the importance of the risk), or they need to be elevated to 'important identified risks' (e.g. if they result in associated additional risk minimization activities).*
- *In certain circumstances, **important identified risks may need to be removed from the safety specification** (e.g. for products marketed for a long time for which risks and the required risk minimization measures have become fully integrated into standard clinical practice thus reducing the risk to a level when is no longer considered an important risk).*
- *Given the overall aim of obtaining more information regarding the benefit-risk balance in certain populations excluded in the pre-authorisation phase, it is expected that as the product matures, the classification as missing information will not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to the areas of missing information. Summary of product characteristics (SmPC) changes should be made accordingly.*

- *Finally, with the exception of some patient registries and programmes (such as pregnancy prevention programmes), over time* ***the additional pharmacovigilance activities in the RMP will be completed and thus removed from the RMP****. The need to continue additional risk minimisation activities may change, as they become part of the routine practice.*

Guidelines to submit a RMP [2]

As per the EMA guidelines,

- In the European Union (EU), companies must **submit an RMP** to the Agency at the time of application for a marketing authorization. For medicines that do not have an RMP, it is likely that one will be required with any application involving a significant change to the marketing authorization.
- In addition, for nationally authorized medicinal products, any National Competent Authority (NCA) in the EU can request an RMP whenever there is a concern about a risk affecting the benefit-risk balance of a medicine.
- RMPs are continually **modified and updated** throughout the lifetime of the medicine as new information becomes available. Companies need to submit an updated RMP:
    - At the request of EMA or an NCA;
    - Whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk-minimisation milestone being reached.

RMPs can only be submitted at the same time as the periodic safety update report (PSUR) if the change in the RMP comes as a consequence of the PSUR.

As per the GVP module V (Rev 2) [1], the submitted RMP should follow the RMP template (please refer to Appendix I for RMP template). The amount of information, particularly in RMP part II, to be provided will depend on the type of medicinal product, its risks, and where it is in its life cycle.

References

1. European Medicines Agency's Guidelines on Good Pharmacovigilance Practice Module V-Risk Management System (Revision 2, dated 24 February 2016). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/02/WC500202424.pdf [Last accessed on May 2019}

2. Risk management Plan. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp [Last accessed on May 2019]