Preparation of a Meaningful and Appropriate Risk Management Plan – a Multifunctional Task

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List of Abbreviations

ADR	Adverse Drug Reaction
BLA	Biologic License Application
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios
CRO	Contract Research Organisation
CTD	Common Technical Document
DCP	Decentralised Procedure
DHCP	Dear Healthcare Professional (Letter)
EMA	European Medicines Agency
EPPV	Early Post-Marketing Phase Vigilance
ETASU	Elements to Assure Safe Use
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
ICDB	Integrated Clinical Database
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
KFDA	Korean Food and Drug Administration
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRP	Mutual Recognition Procedure

NCE	New Chemical Entity
NDA	New Drug Application
PASS	Post-Authorisation Safety Study
PEM	Prescription Event Monitoring
PIP	Paediatric Investigational Plan
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
PUMA	Paediatric Use Marketing Authorisation
QA	Quality Assurance
QPPV	Qualified Person for Pharmacovigilance
REMS	Risk Evaluation and Mitigation Strategy
RiskMAP	Risk Minimisation Actions Plan
RMP	Risk Management Plan
SOC	System Organ Class
SmPC	Summary of (medicinal) Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutics Goods Administration
US	United States

The terms RMP and EU-RMP are used synonymously.

1 Introduction

1.1 Role of risk management plans in pharmacovigilance

During the past years, risk management has become an important tool for industry as well as for regulators. In particular, pharmaceutical companies as well as regulatory authorities have placed increasing emphasis on how to detect, manage and communicate risks, as not everything is known about the safety of newly approved medicinal products because clinical trials are not able to detect rare drug-induced adverse events at the time of approval (Weaver et al., 2008, Walton and Heffernan, 2010). As medicinal products are subject to strict regulation throughout the product life cycle, pharmaceutical companies have to provide evidence that their product is effective and safe (Banerjee and Barr, 2007).

The awareness of patient safety and protection of public health is reflected in several laws which explicitly refer to the need for dedicated risk management systems.

According to *Directive 2001/83, Article 8(3) (ia)* for national or decentralised approved medicinal products: "The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I: A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce."

For centralised approved medicinal products *Regulation 726/2004, Article 9(4)* comes into force as part of the positive CHMP opinion: If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:

(b) "details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Title VI of Directive 2001/83/EC"

(c) “details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product”.

As stated in *Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use* – a Risk Management System is required: “The description of a risk management system should be submitted in the form of an EU-RMP (Part I. 3.3: EU-RMP)”.

On 14 November 2005, the Committee for Medicinal Products for Human Use (CHMP) incorporated and enhanced ICH E2E by establishing the “*Guideline on Risk Management Systems for Medicinal Products for Human Use* (which is included as chapter 1.3 of Volume 9A) – a new European legislation that authorises regulatory authorities to require pharmaceutical companies to submit, along with their application for marketing authorisation, a risk management plan comprising detailed commitments to post-authorisation pharmacovigilance (CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use, 14 Nov 2005, and Frau et al., 2010).

A Risk Management Plan (RMP) represents a summary of the safety profile, important identified risks (e.g. populations at risk) and important missing information (e.g. populations in which the product might be used) concerning a medicinal product for human use and constitutes a regulatory instrument for dealing with anticipated risks of human medicinal products (Dictionary of Pharmaceutical Medicine, 2009). The RMP has to be submitted as part of the core dossier with the application to the regulatory authorities in Module 1.8.2 in the Common Technical Document (CTD). An RMP can be submitted as a stand-alone document with Annexes at any time of the product life cycle e.g. during preclinical testing, pre-approval clinical development or post-approval (referenced in the Periodic Safety Update Report (PSUR)), but specifically:

- For Marketing Authorisations for a New Chemical Entity (NCE)
- For Marketing Authorisations for Biosimilars

- For Marketing Authorisations for a generic/hybrid product (where the reference product comprises an RMP with ”additional risk minimisation activities”)
- For Paediatric Use Marketing Authorisations (PUMA)
- For Marketing Authorisations for a new dosage form, indication (including new patient population) or manufacturing change of a biological product (as long as there is no exception granted)
- At the request of a regulatory authority
- At the initiative of the Marketing Authorisation Holder (MAH)
- On demand during a scientific advice or a pre-submission meeting

The main function of the RMP is to improve pharmacovigilance by identifying potential safety issues of human medicinal products, presenting how to reduce these risks and consequently to increase the knowledge about the human medicinal product concerned. Creating an RMP is a complex, challenging and cross-functional process that focuses on evaluating safety issues identified during product development.

The aim of this master thesis is to illustrate the contribution of different departments within a pharmaceutical company for the development of an RMP. It will be discussed which aspects could be improved for a more efficient interaction of all disciplines concerned, what has to be considered during the planning of the RMP preparation.

1.2 Structure of the master thesis

This master thesis will focus on the contribution of different departments of pharmaceutical companies for the preparation of a meaningful and appropriate EU-RMP. A comparison of the EU-RMPs to other regulated countries like the United States, Japan and Australia will be drawn. Furthermore, RMPs for medicinal products used in children will be highlighted as well as RMPs for biopharmacological products, as for biopharmaceutics specific aspects have to

be considered. In addition, it will be assessed which key aspects have to be considered for the preparation of educational material for health care professionals and for patients as well as for the submission of an EU-RMP. Finally, it will be investigated to what extend a good planning in terms of time management and other aspects like the involvement of affiliates, licensing partners and financial impacts will lead to an efficient and successful coordination and collaboration between the concerned departments.

2 Existing research on RMPs

2.1 Summary of main findings so far

The international scientific literature concentrating on RMPs in particular mainly consists of a limited number of publications. Overall, multiple articles give attention to common questions regarding pharmacovigilance and Risk Management in general and to some extent cover RMPs as well. The key results of the most important questions constitute that RMPs need continuous adjustment and further development and that there is relatively sparse information available on how RMPs are evaluated by regulatory authorities.

In the following a short summary is given of the most relevant articles. Carbarns et al. (2007) describes in detail the content of the EU RMP with special focus on the Risk Minimisation Plan. The authors conclude that early epidemiological profiling of target diseases and targeted pharmacoepidemiology studies to characterise risks should be used to a large extent. Bush et al. (2005) describe the different practices of Risk Management (e.g. clinical studies, spontaneous reporting, risk communication) used in the US. The authors pay special attention to prescription event monitoring (PEM) and epidemiological databases used in the US. Giezen et al. (1) (2009) demonstrate the importance of post-authorisation safety studies (PASSs) as shown in a comparison of EU-RMPs for biological products and small molecules. In a study conducted over the period 2005-2007, significantly more PASS were proposed for biologics than for small molecules and it was found that only limited study protocols were provided. The authors emphasise the need for more complete study proposals to be submitted earlier on in the evaluation period in PASS. Frau et al. (2010) analysed the characteristics of RMPs for 15 medicinal products approved by the EMA and their impact on post-authorisation safety issues. They identified several critical points in the way RMPs have been implemented, in particular that a couple of activities proposed by the RMPs, such as sufficient communication of risks to practitioners and to the public, do not seem to be adequate in dealing with potential drug risks. Banerjee and Barr (2007) revealed that despite substantial

progress there is still room to improve the effectiveness of risk minimisation as addressed in the RMPs in terms of more focused safety specifications, earlier and more effective cross-functional planning of programme roll-out as well as better post-launch evaluations and ongoing improvement. Key et al. (2010) stated – after developing an electronic database for medicinal products approved via the centralised system in order to track RMPs – that an RMP is the outcome of a compromise between the ideal solution and the realities of post-marketing surveillance and factors that need to be considered including costs, the limitations of spontaneous reporting and signal detection as well as the incidence of any reported adverse event, and aimed to reach a realistic and workable plan for all parties involved. Walton and Heffernan (2010) studied the impact of EU-RMPs on industry and regulatory authorities by conducting interviews with personnel who is experienced with the implementation of RMPs. During the interviews with pharmaceutical companies and regulatory authorities incl. EMA, it appeared for some respondents that RMPs constitute an excessive burden on their organisations, while in contrast, for some authorities RMPs created an increased workload with regard to the assessment and follow-up. Sharrar (2008) stated that risk management guidelines often are differently interpreted which leads to disagreement over the same safety data as e.g. the definition of adverse reactions still leave room for personal interpretation.

2.2 Gaps in existing research

While the abstracts presented above deal basically with the implementation and the review of RMPs or assess their impact on post-authorisation safety, to date no publication in the scientific literature can be found specifically on the planning and preparation of RMPs. Only sparse research exists on RMPs in particular.

This subject was chosen for the master thesis because the preparation of RMPs constitutes a cross-functional task of increasing importance for the day-to-day business of a pharmaceutical company. The aim of this master thesis is to illustrate the contribution of the different departments within a pharmaceutical

company for the development of an RMP. The results of this master thesis will make a contribution to the meaningful and well organised preparation of an RMP.

3 Developing an EU-Risk Management Plan

3.1 Owner of the EU-Risk Management Plan

As different departments of a pharmaceutical company make their contribution to the preparation of an EU-RMP in terms of providing updated data in a pre-determined period, it is reasonable to assign one dedicated person as the owner of the EU-RMP instead of an entire department. The dedicated person should have knowledge of the history of the origins of the EU-RMP as well as of the legal basis and should make a realistic estimation of the resources of all involved parties for the preparation. In addition, the RMP officer - acting as the dedicated person - should establish a multidisciplinary RMP implementation team in order to coordinate the activities with regard to time planning and to finalise the EU-RMP within the agreed timeline. For this purpose, the RMP officer should be equipped with adequate authority. Meetings at regular intervals help to coordinate and align the work of all involved members and also serve as a platform for the exchange of opinions. As the EU-RMP is part of the pharmacovigilance activities, the RMP officer can be nominated preferably from the clinical department or, after authorisation – when there is more safety data available – from the pharmacovigilance department, for this purpose for the RMP prepared for a medicinal product that is on the market. It must be ensured that the RMP officer has access to all safety data available to this date. For medicinal products to be submitted initially to the authority, it is more important that the RMP officer has a profound knowledge of clinical development. To this end a medical expert may function as an RMP officer.

3.2 Structure of the EU-Risk Management Plan

3.2.1 Overall structure

The "*Guideline on Risk Management Systems for Medicinal Products for Human Use*" proposes a clear structuring of the EU-RMP by means of a template.

The EU-RMP is divided into two parts:

- Part I contains:
    - A Safety Specification
    - A Pharmacovigilance Plan
- Part II contains:
    - An evaluation of the need for risk minimisation activities
    - And if there is a need for additional (non-routine) risk minimisation activities: A risk minimisation plan

Prior to Part I, according to the EMA Template for EU-RMPs must start with a general overview, presenting the product details. Prior to this, in terms of a better tracking, a version control of the document including the reason for the update has to be provided. In addition, a short summary of the changes in the revised RMP naming the sections which were revised and/or amended is recommended. These administrative tasks should be undertaken by the person or department which is responsible for the final formatting and submission of the EU-RMP, e.g. Regulatory Affairs and should be verified by the Quality Assurance (QA) department.

In the following section, content and specifications of each part of the EU-RMP will be discussed.

3.2.2 Product details

The "product details" section presents the core information of the medicinal product concerned and gives a general overview of the product. This section requires data from different sources which can be compiled by the regulatory affairs department as information regarding approval procedure and – if applicable – of the approval dates are part of the initial submission. Additional data like proposed or approved indications will be provided by the clinical research department in coordination with the regulatory affairs department. The date for the preparation of the EU-RMP and information concerning the approval procedure and the dates of authorisations should be provided by the regulatory affairs department as detailed information is required regarding the

approval. This information can be derived from the initial submission or – if applicable – from the approval letter.

3.2.3 Part I: Section I – Safety Specification

3.2.3.1 Overall content

The section "safety specification" represents one of the two elements in Part I of the EU-RMP and provides a summary of important potential or identified risks related to the product, especially describing important missing information. The safety specification is seen as the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan according to the "*Guideline on Risk Management Systems for Medicinal Products for Human Use*" (2005), abbreviated as Risk Management Guideline. This section should give guidance to the applicant or MAH as well as to the regulatory authorities to help identifying gaps at the time of submission of the EU-RMP, especially with regard to which patient groups were not studied, special risk factors and which events can be expected in the target patient population, as well as facilitate the preparation of the following sections.

3.2.3.2 Non-Clinical Findings (RMP section 1.1)

This section requires information concerning the medicinal product derived from the preclinical research and technical development. The main objective is to provide a statement if safety issues that could be relevant for the clinical development emerged from nonclinical testing. The relevance of the findings to the use in humans should be considered. It should be outlined e.g. by means of a tabulated listing, which safety concerns have not been adequately addressed by clinical data or which are of unknown significance. In addition, it should be specified if there is a need for additional non-clinical data if the product is used in special populations (e.g. for the use in children this would mean additional data in juvenile animals to investigate the effect of the medicinal product on the developing organs).

The results of the non-clinical findings should be listed including all relevant non-clinical studies, such as single-dose toxicity studies, repeated-dose toxicity studies, safety pharmacology studies (e.g. with special regard to QT interval prolongation) and toxicology studies (including nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, and reproductive toxicity), in-vitro studies, studies investigating the cytochrome P450 activities, pharmacokinetic studies including distribution and drug interaction studies and – if relevant – studies in juvenile animals, if there are findings that show relevance for developing organ systems. Specifically for biopharmaceuticals, preclinical studies regarding immunogenicitiy could be relevant for the use in humans – also affecting the clinical development – and their results should be presented. These data will usually be provided by the nonclinical safety department and other preclinical departments like drug metabolism and in-vitro/in-vivo pharmacology, in collaboration with the technical development.

With regard to the time planning, it is reasonable to file on a regular basis the preclinical study reports electronically e.g., on a central drive to which the RMP owner has access. In case Contract Research Organisations (CROs) are assigned to conduct animal or other preclinical studies for pharmaceutical companies, an effective agreement should be made concerning the time management of providing up to date finalised study reports to the sponsor.

In addition, it is recommended to screen the scientific literature periodically and – if necessary – take into account relevant preclinical results from these abstracts and their implications for the EU-RMP.

3.2.3.3 Clinical Findings

3.2.3.3.1 Overall content

This section presents an overview on safety specifications derived from the use of the medicinal product in humans. Here, the overall information regarding clinical safety data is presented.

3.2.3.3.2 Limitations of the human safety database (RMP section 1.2)

Regarding human safety databases, many pharmaceutical companies have established an integrated clinical data base (ICDB) which includes all safety data resulting from clinical trials for a medicinal product irrespective of their relatedness. However, as these data are limited in terms of the size of the study population, these data illustrate only one part of the entire safety profile that is gradually complemented after market introduction of the medicinal product.

Clinical Trial Exposure – Listings

The template of the Risk Management Guideline indicates tabulated listings including all clinical trials (double-blind/open label/comparator) with special regard to the exposure. However, the categories provided within the template are suggestions only. The template indicates that the listings should be tailored to the product, clearly identified and justified.

It is common use that pharmaceutical companies have clinical trial databases in place that include all clinical trials. A clinical trial database usually lies within the responsibility of the department that is responsible for the management and the co-monitoring of clinical studies, e.g., clinical operations. Listings generated from the clinical trial databases generally display the core study information such as the study number and the phase, duration of the treatment (in weeks), treatment arm, and the exposure in terms of months or years. The listings must indicate the number of patients that were included in the studies in total and the number of patients treated with the medicinal product of interest. In addition, it should be stated if a clinical study was prematurely discontinued for safety reasons.

The tabulated listing in the clinical trials exposure section should present all finalised clinical trials divided by indication. In addition, one listing presents only randomised clinical trials, the other listing includes all studies including open-extension study periods. Further listings should group the studies by age and gender or by dose. For this purpose, it is helpful to integrate a copy of the

listings extracted from the clinical trial database because manually created listings may be error-prone.

For a good time planning, the listings should be generated soon after the cut-off date and for study data to be included in the RMP.

More detailed attention should be given to special populations presented in a separate listing. Here it should be indicated if pregnant or lactating women were exposed to the medicinal product. If so, the number of pregnancies should be clearly explained, and if already known, the outcome. In addition, it should be stated if a new safety issue arises from the pregnancies for the medicinal product. If pregnant or lactating women were not included in any study, e.g. because the study population includes only elderly patients, this should be stated. Other special populations like patients with renal, hepatic or cardiac impairment should be presented as well as other sub-populations.

Exposure in a paediatric population should be displayed separately. If the medicinal product was not investigated in children below 18 years, relevant articles and their implications regarding safety, e.g., the type of adverse events reported in this population, should be taken into account in this section.

Epidemiological study exposure

The exposure of epidemiological studies should be presented, if applicable. In this subsection, a table with information regarding the type of study, population studied, the duration, the number of patients and the patient time should be provided.

The information regarding epidemiological studies is provided by the epidemiology department in collaborations with medical biometrics, data management and clinical operations.

Post authorisation exposure

If applicable, this section presents the exposure data after market introduction of the medicinal product. The exposure is calculated on the basis of the

clinical trials performed (post-authorisation) and on the sales data since first marketing approval. The cut-off date for the RMP serves also as the cut-off date for the exposure data.

Information regarding exposure data can be provided by the department responsible for the preparation of the PSURs, e.g. the pharmacovigilance department, as the exposure data have to be presented in each PSUR as well. The exposure data are usually generated from applications for business processes – owned by the Controlling department - including sales data.

The information regarding section 1.2 of the RMP is provided by the medical expert in collaboration with the medical biometrics, data management and clinical operations.

3.2.3.4 Populations not studied in the pre-authorisation phase (RMP section 1.3)

Special attention must be paid to patient populations that have not been studied during the clinical development of the medicinal product in terms of the exclusion criteria and the populations which were effectively investigated. It should be stated if the exclusion criteria are addressed in the SmPC. Where exclusion criteria do not present contraindications to the treatment this should be clearly stated and justified. Patient populations that have not been investigated should be tabulated such as e.g., paediatric population, elderly patients, pregnant or lactating women, patients with relevant co-morbidity (renal, hepatic or cardiac impairment), patients with more severe diseases than those studied in the clinical development, sub-populations with genetic polymorphisms or patients of different ethnic origins.

This section is clearly assigned to the medical experts in collaboration with the medical biometrics department and potentially the pharmacovigilance department as here medicinal evaluation and justifications have to be given.

3.2.3.5 Post authorisation experience (RMP section 1.4)

If applicable, the post authorisation experience section presents an overview on the regulatory activities for the medicinal product. In this section details on

changes to the indication, planned treatment pattern, estimated population drug usage over time, place in treatment and market position have to be provided for the initial submission of the RMP. In addition, the overall use in terms of the world-wide exposure (in patient years) to the medicinal product of interest should be given. Furthermore for RMP updates, regulatory actions taken (on the request of the regulatory authority or by the applicant or MAH) have to be listed in form of a tabulated listing, sorted by issue, country, actions taken and date. If no actions were taken, this should be clearly stated and justified.

For this section, the regulatory affairs department should provide the updated data, supported by the department providing the exposure data (Controlling), the medical experts, the pharmacovigilance department and medical affairs.

3.2.3.6 Adverse events and adverse reactions (RMP section 1.5)

This section is divided into two subsections, one for newly identified safety concerns and one for details of important identified and potential risks (including newly identified). For the newly identified safety concerns, the RMP-template asks for a tabulated listing, sorted by the number of safety concerns. In the tabulated listing, details on the safety concern, as well as the source and implications for product literature should be listed. In addition, it should be stated if new clinical studies were proposed in the pharmacovigilance plan and if new risk minimisation actions are planned.

The second subsection provides an overview of the details of important identified and potential risks including newly identified risks. According to the RMP template, a tabulated listing has to be provided. The following additional information has to go along with the identified and potential risks presented as MedDRA PT term: seriousness and outcome, severity and nature of the risk, the frequency with 95% Confidence Interval (CI), background incidence and prevalence, risk groups or factors, potential mechanisms, preventability, potential public health impact of safety concern, evidence source and regulatory actions taken.

This section requires close interaction between the pharmacovigilance department and the medical experts as here detailed information regarding safety as well as potential mechanisms have to be provided. For this section, a line listing generated from a safety database is helpful for the evaluation presented in the tabulated listing.

3.2.3.7 Identified and potential interactions with other medicinal products, food and other substances (RMP section 1.6)

For this section, the EU-RMP template asks for a tabulated listing for each important drug or food interaction in terms of the interacting substance, effect of interaction, evidence source, possible mechanisms and potential health risk, followed by a discussion.

Information provided by medical experts – especially from the phase I clinical studies unit – potentially in collaboration with the pharmacovigilance department – has to be presented. If a medicinal product – proven by clinical and preclinical studies – is not distributed systemically in the human organism and acts only locally where no interaction is suggested, this has to be stated.

3.2.3.8 Epidemiology of interaction(s) and important adverse events (RMP section 1.7)

This section which is divided into three subsections focuses on detailed information regarding the indication and important adverse events. In the first subsection, a tabulated listing for each indication with the following information has to be provided: Indication/target population, incidence of target indication, prevalence of target indication, the mortality in target indication, potential health risk and a demographic profile of target population has to be specified. For the second subsection, for each indication important co-morbidity in the target population has to be discussed. In the third subsection, for each identified or potential risk, the epidemiology of the condition in the target population has to be provided when unexposed to the product with regard to the incidence of condition, prevalence of condition and mortality of condition. In this context, reference should be made to clinical

studies and publications if sufficient data can not be provided by the applicant or MAH.

The information in this section is provided primarily by the medical experts with special focus on epidemiology, potentially supported by the pharmacovigilance department. In addition, a literature search to support the data provided in the section should be carried out by the applicant/MAH or an external provider.

3.2.3.9 Pharmacological class effects (RMP section 1.8)

In this section each identified risk which is believed to be common to the pharmacological class has to be presented in the form of a tabulated listing with special regard to the frequency in clinical trials and the frequency seen with other products in the same pharmacological class, followed by the applicant/MAH's comment. For this purpose, a systematic literature search is highly recommended.

This section gives an overview on class effects with regard to the medicinal product of concern. The evaluation in this section is provided by the medical experts, the medical biometry, data management, library and the pharmacovigilance department.

3.2.3.10 Additional EU requirements (RMP section 1.9)

Special attention has to be paid to the following aspects in this section according to the RMP template: Potential for overdose, for transmission of infectious agents, for misuse for illegal purposes, for off-label use and for off-label-paediatric use. This section summarises the overall experience with the medicinal product in question. Information derived from the medical experts, pharmacovigilance, regulatory affairs, technical development and the medical affairs department is needed to specify in detail the potential of these risks.

3.2.3.11 Summary – ongoing safety concerns (RMP section 1.10)

The RMP template requires listing the important identified risks, important potential risks and important missing information requiring input from the medical experts and the pharmacovigilance department for this section.

3.2.4 Part I: Section II – Pharmacovigilance Plan

3.2.4.1 Overall content

The pharmacovigilance plan is based on the safety specification and covers actions intended to identify and characterise safety concerns.

3.2.4.2 Routine pharmacovigilance practices (RMP section 2.1)

This section presents a summary of the routine pharmacovigilance system by specifying the processes which are described in the detailed description of the pharmacovigilance system (CTD section 1.8.1). The processes usually include the collection and medical evaluation of Individual Case Safety Reports (ICSRs), expedited reporting of adverse drug reactions (ADRs) and suspected unexpected serious adverse reactions (SUSARs) to the competent authorities in a predetermined period, regular signal detection and signal evaluation, weekly or monthly screening of the scientific literature for ADR reports, maintenance of the pharmacovigilance quality management system and standardised processes to define and decide on adequate measures for crisis management and risk minimisation. A cross-reference to the respective section in Module 1 of the CTD should be made if the application is made via the centralised procedure.

This summary of the routine pharmacovigilance system should be provided by the pharmacovigilance manager in agreement with the Qualified Person for Pharmacovigilance (QPPV).

3.2.4.3 Summary of safety concerns and planned pharmacovigilance actions (RMP section 2.2)

For this section, the RMP template asks for a tabulated listing for each safety concern with the respective planned action(s) taking into account important

identified risks, important potential risks and important missing information. Planned actions comprise a regular follow-up of ADRs that present an important identified risk, regular and specific reporting of these ADRs in PSURs. Newly available results for updates to the pharmacovigilance plan must be included. When no action beyond the routine pharmacovigilance activities is planned, this has to be justified.

The information presented in this section is to be provided by the pharmacovigilance department in agreement with the QPPV and coordinated with the medical expert.

3.2.4.4 Detailed action plan for specific safety concerns (RMP section 2.3)

This section provides an overview on the detailed actions for each important identified or potential risk or missing information. According to the RMP template, a listing with regard to the objective and rationale of the proposed actions, further measures which may be adopted resulting from this action and the decision criteria for initiating such measures, milestones for evaluation and reporting including justification for choice of milestones and the title of protocols if applicable have to be presented.

Depending on the type of actions detailed provisions have to be made e.g. by technical, pre-clinical or clinical development and/or by the pharmacovigilance, medical affairs, epidemiology or supply chain department.

3.2.4.5 Overview of study protocols for the pharmacovigilance plan (RMP section 2.4)

In this section, a general overview of clinical trials is given in a tabulated listing in accordance with the RMP template. The study number, protocol version and status, the planned date for submission of interim data and the planned date for submission of the final data have to be displayed where applicable.

The information regarding the clinical trials for this section is usually provided by the medical experts in coordination with biometry and data management, and clinical operations.

3.2.4.6 For updates to the EU-RMP (RMP section 2.5)

In case of an update of the EU-RMP, when safety studies were planned in the previous version of the EU-RMP, the results have to be presented in this section including a summary of newly available results and implications of all available data for the safety concern taking into account important potential, identified risks as well as important missing information. If available, the final study report should be appended and a cross-reference should be provided.

This task has to be undertaken by the medical experts, epidemiology, regulatory affairs, medical affairs and if applicable in collaboration with the pharmacovigilance department.

3.2.4.7 Summary of Outstanding Actions, including Milestones (RMP section 2.6)

If actions are planned, e.g., additional clinical trials, these have to be listed in form of a tabulated listing stating the milestones/exposure and calendar time and the study status. If no actions are planned this has to be stated.

This section has to be generated by the clinical research department (including medical experts, medical biometry, data management, epidemiology and clinical operations) potentially in collaboration with the pharmacovigilance department, and if applicable with the medical affairs department when post-authorisation actions are planned.

3.2.5 Part II: Section I – Evaluation of the need for risk minimisation activities

3.2.5.1 Overall content

The evaluation for the need for risk minimisation activities should cover all safety concerns specified in the summary of the ongoing safety concerns in Part I of the EU-RMP (safety specification). In this section it must be

evaluated and justified whether routine risk minimisation activities in terms of labelling, product information and packaging will be sufficient or if additional risk minimisation activities will be required (specific educational material or training programmes for prescribers, pharmacists or patients or restricted access programmes etc). When there is a need for additional risk minimisation activities, a risk minimisation plan must be in place. It must be justified when there is no risk minimisation plan in place for a safety concern.

3.2.5.2 Summary table of planned actions for each safety concern (RMP section 3.1)

In this section of part II of the EU-RMP, the safety concerns with regard to important identified risks, important potential risks and important missing information must be listed in tabular format and it has to be stated if the routine risk minimisation activities are sufficient and if so, a description of routine activities with a justification should to be given.

The information presented in this section must be prepared by the departments concerned, e.g. by technical, pre-clinical or clinical research development and/or by pharmacovigilance, medical affairs, epidemiology or supply chain.

3.2.5.3 Potential for medication errors (RMP section 3.2)

According to the EU-RMP template, this section requires a detailed description of the likelihood of medication errors. During drug development the applicant/MAH needs to consider potential reasons for medication errors in terms of naming, presentation, instructions for use and labeling. Respective items identified during the drug development process should be discussed and information regarding the potential cause and the possible remedies should be provided. Evidence should be given how these items were considered for the final product design.

In the post-authorisation phase, it should be discussed how to limit the occurrence of adverse events related to medication errors in the updated EU-RMP. In addition, a statement should be provided if the adverse events relating to medication errors are adequately reflected in the current SmPC.

If a medicinal product shows life-threatening potential when administered by an incorrect route, it must be outlined in which way such administration may be prevented, especially when the medicinal product is administered together with other medicinal products in a potentially hazardous way. It should be discussed if there is a need for visual or physical differentiation among strengths of the same medicinal product and among other medicinal products administered simultaneously. Special attention with regard to medication errors must be given when the medicinal product is meant to be used by visually impaired patients. In addition, it should be made sure that there can be no medication error caused by a pharmacist.

In general, a statement is required with regard to accidental administration or other unintended use by children.

This section requires detailed information regarding medication errors which falls under the responsibility of the medical affairs department and the medical experts, supported by the regulatory affairs department and if applicable with pharmacovigilance.

3.2.6 Part II: Section II – Risk minimisation plan (RMP section 4)

The Risk minimisation plan has to be provided if there is a need for additional (non-routine) risk minimisation activities. The EU-RMP template asks for a tabulated listing for each important identified or potential risk with regard to routine risk minimisation activities (product information, labeling and packaging) and additional risk minimisation activities. For each safety concern, a short description of what to state in the SmPC, labeling, etc. to minimise the risk must be provided as well as an objective and rationale, proposed actions, criteria to be used to verify the success of proposed risk minimisation activity and a proposed review period. Regarding the risk minimisation activities it should be differentiated between the provision of educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes and other risk minimisation activities.

Risk minimisation elements can comprise:

- the performance of a pregnancy test prior to the next prescription when the medicinal product shows teratogenic potential
- the patient signs an informed consent after instruction by the physician
- special prescription status (e.g. for medicinal products with abuse potential)
- supply chain control
- promotional practice restriction
- dispensing only in hospitals
- administration only by physicians or pharmacists
- provision of educational material for physicians and patients incl. SmPC and patient information
- restriction of package size and units (especially for analgetics)
- limited validity of prescriptions
- the use of patient registries

The input regarding the risk minimisation plan requires close interaction of the departments concerned, e.g., technical, pre-clinical and/or clinical research development, pharmacovigilance, medical affairs, epidemiology or supply chain.

3.2.7 Summary of the EU Risk Management Plan (RMP section 5)

For the summary of the EU-RMP the template asks for a tabulated listing with the following information for each safety concern: Proposed pharmacovigilance activities (routine and additional) and proposed risk minimisation activities (routine and additional).

This section should be compiled by the medical expert taking into account the information provided in the pharmacovigilance plan and in the risk minimisation plan when the RMP is prepared for initial submission. For RMPs

submitted after approval, this section requires data provided by the pharmacovigilance department.

3.2.8 Contact Person for this EU-RMP (RMP section 6)

For this section, the responsible person for the EU-RMP has to be specified in terms of name, position, qualification and a signature has to be provided. If there is more than one responsible person, usually one of these two people in charge should be the QPPV as this position requires the overall responsibility with regard to safety for the medicinal product.

This information can be provided by the regulatory affairs department, as the contact person is also required to be listed in the application form of many submissions (e.g. initial applications, line extensions, variations, etc.).

3.2.9 Annexes

The annexes to be provided are listed in the last section of the EU-RMP template. The interface between EU-RMP and EudraVigilance which has to be provided in electronic format for centrally authorised medicinal products, has to be obtained either by regulatory affairs or by the pharmacovigilance department as well as the protocols for proposed and ongoing studies from the pharmacovigilance plan. The current or proposed SmPC and package leaflet should be delivered by the regulatory affairs department as the regulatory affairs department must have the general oversight of the current SmPC and package leaflet. The clinical research department should provide the synopses of ongoing and completed clinical trial incl. large outcome studies, safety and efficacy studies, studies in special subgroups and paediatric studies, synopses of ongoing and completed pharmaco-epidemiological study programs and newly available study reports. The details of a proposed educational program need to be delivered by the medical affairs department, if applicable. Different departments may be responsible for the delivery of “other supporting data” depending on the type of data.

4 Educational materials

In cases where routine safety measures are not sufficient or when the medicinal product belongs to a special product class e.g. drug formulations with abuse potential (e.g. analgetics or sedatives) or products that require exceptional commitment by the patients (e.g. for the use of contraceptives or for specific diseases like Diabetes) additional activities like the preparation of educational material for physicians and patients may form a part of the RMP and related risk minimisation activities.

Educational materials present risk minimisation elements provided to health care professionals and patients for the purpose of providing diligent instructions on the medicinal product for the approved indication and route of administration. The preparation or a revision is usually linked to specific risks regarding abuse, misuse or potential medication errors or to newly detected risks respectively. Educational material is in general prepared by the medical affairs department in cooperation with medical experts and potentially the pharmacovigilance department. In addition, medical affairs usually initiate the distribution of the educational materials to health care professionals. They can be made available to health care professionals via sales representatives, via e-mail or via mail. Educational material has the aim to reduce the frequency and/or severity of adverse events connected to the use of a medicinal product and/or may inform about adequate therapy of adverse events.

It is in the responsibility of the attending physician to pass educational materials on to patients and inform about any risk. Table 1 specifies the provision of the educational materials for an RMP.

It must be considered that in many European countries educational materials require approval from the national authorities prior to distribution to health care professionals and patients. In this context, the MAH must pay attention to the harmonised translations of the educational materials in case the medicinal product was approved via the Mutual Recognition Procedure (MRP) or via the Decentralised Procedure (DCP).

In addition, it is important that the MAH decides whether the educational material should be made available to health care professionals and patients only during the introduction phase of the medicinal product or if the educational materials should form an inherent part of every package.

Table 1: Educational material for an RMP

Educational material for patients	**Educational material for health care professionals**
Visual aids like CD-Roms	DHPC letters
Patient information with special focus on route of administration, contraindications and adverse events, or storage at home	Additional explanations concerning the contents of the SmPC
Educational slides or graphs	Checklists
Brochures	Prescribing/Dispensing Guides

5 RMPs for specific products

5.1 RMPs for biopharmacological products

Although the first recombinant insulin was approved in 1982, biopharmaceuticals are seen as a relatively new class of drugs in the treatment of chronic or severe diseases (Giezen et al. (2), 2009). Biopharmaceuticals are biologically active molecules derived from living cells (Zuniga and Calvo, 2010). They have specific characteristics that can influence their safety profile due to their complex production and purification processes, limited predictability of preclinical data to clinical data due to species-specific action and a high potential for the formation of antibodies which may lead to immunogenicity (Giezen et al. (2), 2009). Due to these specific characteristics, pharmacovigilance activities and risk management required for biopharmaceuticals might differ from those required for small molecules. The TeGenero case in 2006 explicitly illustrates the limited predictability of preclinical data. A cytokine storm occurred in six healthy male volunteers in a phase I trial treated with the superagonist anti-CD28 monoclonal antibody TGN1412. This acute life-threatening adverse event (AE) had not been observed in preclinical trials (Suntharalingam et al., 2006). Due to the limited data from animal studies and due to clinical trials with small numbers of patients, with restricted population in terms of age, gender and ethnicity, with restricted co-morbidity and co-medication, with a relatively short duration of exposure and follow-up at the time of authorisation, data gathered after market entry of such products e.g. through post-authorisation safety studies (PASSs) constitute a valuable and meaningful complement to clinical trials (Sticker and Psaty, 2004). PASS are an important tool for the identification and quantification of safety hazards related to the use of biopharmaceuticals and are defined as a pharmacoepidemiological study (non-interventional) or a clinical trial (interventional) (Giezen et al. (2), 2009). As the formation of antibodies is the main safety problem in context with biopharmaceuticals, PASSs mostly focus on immunogenicity as the immunogenic potential can be affected by many factors like impurities, structural changes, factors related to

the patient's human leucocyte antigen (HLA) type and immunity. Registries have turned out to be beneficial data sources for a PASS.

Another significant safety issue concerning biopharmaceuticals is the categorisation of adverse events in the system organ class (SOC). While adverse events mainly occur with the use of small molecules in the system organ classes "hepatic disorders", "cardiac disorders" or nervous system orders", most of the adverse events occurring with the use of biopharmaceuticals are assigned to the system organ classes (SOC) "general disorders", "administration site conditions" and "infections and infestations" due to predominantly intravenous administration. These differences may have a special impact on the risk management for biopharmaceuticals (Giezen et al. (3), 2008).

The complex production and purification process of biopharmaceuticals may lead to serious adverse events. Therefore, activities to trace batch numbers must be taken into consideration.

In summary, it is mandatory for biopharmaceuticals and biosimilars to have an RMP in place. Pharmacovigilance activities can be routine (spontaneous reporting) or additional, e.g., PASS. An RMP for biopharmaceuticals should focus on the identification of immunogenicity risks and the implementation of special post-authorisation surveillance (Zuniga and Calvo, 2010). Since changes in the purification and production process could influence the safety profile, it is mandatory to ensure clear identifiability of products and batches.

5.2 RMPs for medicinal products used in children

One of the challenges in drug development is the paediatric population. The dynamic process starting with the foetal and embryonic phase throughout birth and infancy to puberty and adolescence is the reason why the paediatric population is very vulnerable, especially with regard to adverse events (Mentzer, 2008). Children cannot be regarded as "little adults", thus safety monitoring of medicinal products used in children should be of topmost interest. As research and development is scarcely conducted in children and as

an extrapolation of safety and efficacy data collected in adults does not fully reflect the needs of the paediatric population, and due to the fact that clinical trials in children face little acceptance in society, most of the medicinal products on the market are not tested in and licensed for this age group, especially regarding very young children.

Off-label use is a common practice in the paediatric population, but it does not offer the same quality, safety and efficacy of medicinal products as for adults (Mentzer, 2008). This may result in complications like missing the right dose and the appropriate formulation (Mentzer, 2008).

In 2007, the EU paediatric regulation 1901/2006 came into force. The implementation of this regulation led to a significant change of the clinical development with pharmaceutical companies being obliged to submit a PIP (Paediatric Investigational Plan).

All these circumstances result in the essential requirement that safety and efficacy must be studied in the paediatric population as the “trial and error” principle is not acceptable in this extremely vulnerable population (Mentzer, 2008). Active surveillance in terms of adverse event reporting, in-hospital settings and the follow-up of paediatric patients present effective measures to increase safety information during the clinical development and in the post-authorisation phase, because pharmacovigilance has slowly shifted towards earlier, proactive consideration of risks and potential benefits, leading to a more developed drug safety risk management (Mentzer, 2008).

The EU-RMP takes into consideration the measures and requirements for clinical development in children. The following sections demand contribution with regard to the paediatric population: Exposure in children, populations not studied in the pre-authorisation phase, and accidental administration or unintended use in children. For the preparation of these sections in the RMP, the competent knowledge of the medical experts in close cooperation with the pharmacovigilance department is required. Therefore, the EU-RMP gives a detailed overview on the activities conducted in the past and planned for the future with special regard to the collection of safety data in the paediatric

population and presents an instrument for the overall safety assessment of a medicinal product for authorities.

6 Practical considerations for a successful RMP preparation

6.1 Financial impact

For the preparation of an RMP further aspects have to be taken into consideration like the financial impact for the MAH in terms of authorship costs. It should be clarified prior to the RMP preparation, if the RMP will be prepared in-house or will be outsourced to an external service provider (CRO or a consultant). In addition, costs of implementing the proposed measures of a RMP should be taken into account in the planning phase. If an EU-RMP is considered to be inadequate by the authorities, a delay in marketing approval may generate additional costs. These aspects should be taken into account in concerning budget planning.

6.2 Time planning

As RMPs have become an inherent part of the lifecycle management of a medicinal product it is mandatory to start with the planning of the RMP preparation in an early stage of the development plan. It is therefore recommended that the RMP officer generates a detailed timetable for the RMP preparation. Particular attention should be given to the preparation of the first RMP, as this requires exceptional efforts from all departments involved. Therefore, internal and external resources have to be planned carefully in order to have all data and listings available at the time of start of the RMP preparation. Further updates of RMPs will not necessarily need the involvement of all concerned departments as required for the preparation of the initial RMP. In addition, it should be ensured by the RMP officer that the RMP preparation is coordinated with other submission documents and that regulatory feedback is helpful in order to optimise the format and content.

6.3 Quality Assurance

Another important aspect is the involvement of the quality assurance department in order to ensure that a properly reviewed and sound RMP is

provided to the authority. As for most documents prepared in research and development, it is helpful for this matter to ask the quality assurance department for support. Quality assurance can conduct a quality control check of the final draft of the EU-RMP and all corresponding documents (e.g. annexes, educational material). After the review by quality assurance the final version of the EU-RMP can be sent for review to all concerned department managers for final release.

6.4 Affiliates and Licensing Partners

For pharmaceutical companies with affiliates in other countries, it is mandatory to take into account the role of their affiliates and the implications of the RMP submission in the countries where an application for the medicinal product will be submitted to the respective authorities. It is recommended to inform the regional regulatory teams about the RMP preparation at an early stage to make sure that the affiliates are prepared activities like the distribution of educational materials and the preparation of corresponding translations.

In case of one or more licensing partners, it is recommended to clarify the responsibilities of each party. An RMP can be successfully prepared as a joint effort, but it is necessary to clearly define the roles and to set up a detailed timetable for the provision of information by all licensees to the RMP officer.

All administrative activities listed above should be coordinated by the RMP officer prior to the RMP preparation.

7 EU-RMP – comparison with other regulated countries

7.1 Overall findings

The submission of EU-RMPs is a requirement according to the "*Guideline on Risk Management Systems for Medicinal Products for Human Use"* which came into force in November 2005 incorporating and enhancing ICH E2E, covering all medicinal products for human use authorised within the European Union.

A comparison with other countries – specifically in terms of the development of medicinal products – reveals significant differences in the different legislations.

7.2 United States

In the US, the Food and Drug Administration Amendments Act (FDAAA; PL 110-85) was signed into law in 2007. This law intends to improve drug safety by providing FDA with post-approval authority over medicinal products and biopharmaceuticals through new risk identification and communication strategies (Lofton, 2009). The format for the Risk Evaluation and Mitigation Strategy (REMS) is specified in the *"Guidance for Industry. Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessment, and Proposed REMS Modifications"*, dated September 2009. This law mandates FDA to decide whether REMS is necessary, as part of the approval process or during the post-approval period. FDAAA has given FDA the authority to require REMS for medications or medication classes when necessary to ensure that the benefits of a drug outweigh the risks, but in general the submission of REMS is voluntary by the applicant/MAH in the US. REMS apply to new drug applications (NDA) and biologics licence application (BLA). The proposed REMS can be submitted with the original application, as a supplemental application or as an amendment to an existing original or supplemental application, without having been required to do so by FDA. The basis for requiring a REMS originates from the risk-benefit profile

of the product. If the known or potential risks are significant, a REMS may be necessary. Before FDAAA came into force, a small number of medicinal products were approved by FDA by providing a Risk Minimisation Actions Plan (RiskMAP). Regarding products previously authorised with a RiskMAP, a REMS must replace the RiskMAP if legal requirements for a REMS are met (*Guidance for Industry: Format and Content of proposed Risk Evaluation and Mitigation Strategies, REMS Assessments, and Proposed REMS Modifications, September 2009).*

When comparing the contents of the EU-RMP and the REMS program, the contents of the REMS turn out to be different. As defined in the FDAAA, a REMS has to include different components like a communication plan for the physician, a medication guide for the patient, a patient package insert, and other elements to ensure safe use (ETASU), and it may include an implementation system. The contents of specific REMSs may vary (Lofton, 2009) whereas the content of the EU-RMP is predetermined by the *Guideline on Risk Management Systems for Medicinal Products for Human Use. London, 14 November 2005.* Depending on the severity of the safety risk, FDA may require only one of these elements or a combination of these (Gliklich, 2011).

The lack of predetermined framework requirements for REMS – as they exist for the EU-RMP – is viewed critically. As each REMS is prepared independently by the applicant or MAH, REMS are not standardized in design and implementation which results in a growing number of administrative, logistical and workflow challenges for the health care system in the US. This inconsistency leads to confusion and inefficiency in implementation. This burden on the health care system has the potential to reduce patient access to medicinal products as it may limit provider participation (*White paper on designing a risk evaluation and mitigation strategies (REMS) system to optimize the balance of patient access, medication safety, and impact on the health care system, 2009).*

7.3 Japan

In Japan, a regulation under the Ministry of Health, Labour and Welfare (MHLW) Ordinance was introduced on October 1st, 2001 under the name "Early-Phase Post Marketing Vigilance (EPPV)" and it serves as an example of an early post-marketing RMP (Final Concept Paper, 2002). EPPV constitutes one type of post-marketing condition for new medicinal products and provides a solid basis for better risk and lifecycle management for new medicinal products. To prevent serious ADRs from occurring just after start of marketing, it is obligatory to conduct EPPV – which is part of the conditional authorisation – six months after launch of a new medicinal product. It is a requirement to provide product information which was gained during drug development, to medical institutions and request the proper use of the new medicinal product. Thus, it should be avoided that health care professionals use the products without understanding them. It has to be ensured that necessary information for appropriate use is explained in detail to the medical institutions two weeks before drug delivery. The medical institutions are requested to use the medicinal products carefully and report serious ADRs immediately to the pharmaceutical company.

In addition, the EPPV process helps to formulate risk management measures to address possible serious ADRs by collecting rapid information on them and take necessary safety measures thus minimising the effects of damage caused by ADRs (Doi and Tsuda, 2008). The establishment of the conditional authorisation that lasts four to ten years before undergoing a re-evaluation is intended to increase safety for new medicinal products and lead to a shorter development time.

7.4 Other countries

The Australian authority Therapeutic Goods Administration (TGA) has formally adopted the *EU Guideline Volume 9A*. The requirement for an RMP commenced on 1st April, 2009.

The Swiss authority – Swissmedic – accepts the submission of EU-RMPs as it complies with the ICH concept as well as the submission of a documentation prepared according to the FDA guidelines. In the latter case, Swissmedic recommends to conduct a compliance check of the documentation with regard to ICH-E2E (2004) prior to submission.

Health Canada appreciates the submission of an EU-RMP as a proactive approach outlining actions to prevent or mitigate risks, even though there is no comparable report established yet. Current risk management activities include the creation of product labels and monographs, and package inserts; establishing education for health care professionals and patients and communicating new risks to health care professionals and patients.

In Mexico, it is currently discussed at COFEPRIS (Mexican health authority) to introduce the RMP as a requirement for registration of new molecules.

Many other authorities in developed countries like the Korean Food and Drug Administration (KFDA) established a pharmacovigilance guideline including a set of pharmacovigilance activities designed for the minimisation of drug-related risks.

7.5 Summary

In summary, risk management is exercised in many regulated countries. This circumstance illustrates the increasing importance of introducing a risk management plan or comparable practices. However, within the European Union, the EU-RMP constitutes a specific feature in the pharmacovigilance environment as the applicant/MAH has to follow a predetermined structure which is not necessarily the case outside the EU.

8 Conclusion and Outlook

Every effective medicine is associated with risks. Risk detection, risk assessment, risk minimisation and risk communication are the core elements of risk management. The general purpose of the EU-RMP is to make sure that all risks are actively managed with the aim to protect patients as far as possible from serious adverse reactions (SAE) (MHRA news, 2006).

The preparation of an EU-Risk Management Plans has become mandatory for new medicinal products in 2005 with the introduction of the "*Guideline on Risk Management Systems for Medicinal Products for Human Use"* – a European legislation that authorises regulatory authorities to require pharmaceutical companies to submit an EU-RMP for initial approval or maintenance of new chemical entities or at the request of a regulatory authority.

At the time of approval restricted data is available on the safety of a medicinal product because clinical trials due to their limitations do not present "real-world use" experience. It is therefore essential that post-authorisation data are used as a supplement to the data generated during the clinical development phase in evaluating the safety aspects of a medicinal product. The EU-RMP constitutes a proactive approach to detect and assess risks with the objective to reduce risks by means of risk minimisation activities including adequate risk communication.

Risk management is handled differently from country to country. Not every authority requires a formal risk management plan. Other regulated countries like the United States, Japan and Australia have established risk management systems as well which illustrates the increasing importance of the introduction of risk management – and specifically risk minimisation activities. In most countries, however, the applicant/MAH does not have to follow a fixed structure for the risk management plan as is the case in the European Union for the preparation of an EU-RMP.

Table 2: Contribution of different departments to each RMP section

RMP sections according to the EU-RMP Template			**Contributing department of a pharmaceutical company**
Part I	**Section I – Safety specification**	**1.1 Non-clinical**	Technical Development Non-Clinical Safety (incl. Drug Metabolism In-vitro/In-vivo pharmacology)
		Clinical **1.2. Limitations of the human safety database**	Medical Expert Biometry/Data Management Clinical Operations Controlling (sales data for exposure)
		1.3. Populations not studied in the pre-authorisation phase	Medical Expert Biometry Pharmacovigilance, if applicable
		1.4 Post authorisation experience	Medical Expert Pharmacovigilance Regulatory Affairs Medical Affairs Controlling
		1.5 Adverse events	Pharmacovigilance Medical Expert
		1.6 Identified and potential interactions with other medicinal products, food and other substances	Medical Expert for Phase I clinical studies Pharmacovigilance, if applicable
		1.7 Epidemiology of the indication(s) and important adverse events	Epidemiology Pharmacovigilance Library
		1.8 Pharmacological class effects	Medical Expert Biometry/Data Management Pharmacovigilance Library
		1.9 Additional EU Requirements	Medical Expert Pharmacovigilance Regulatory Affairs Medical Affairs
		1.10 Summary – Ongoing safety concerns	Medical Expert Pharmacovigilance
	Section II – Pharmaco-vigilance Plan	**2.1 Routine pharmacovigilance practices**	Pharmacovigilance (QPPV)
		2.2 Summary of safety concern and planned pharmacovigilance actions	Pharmacovigilance (QPPV) Medical Expert
		2.3 Detailed action plan for specific safety concerns	Technical Development Pre-clinical Development Medical Expert Pharmacovigilance Medical Affairs Epidemiology Supply Chain
		2.4 Overview of study protocols for the	Medical Expert Clinical Operations

RMP sections according to the EU-RMP Template			Contributing department of a pharmaceutical company
		pharmacovigilance plan	Biometry/Data Management
		2.5 For updates of the EU-RMP	Medical Expert Pharmacovigilance, if applicable Regulatory Affairs Epidemiology Medical Affairs
		2.6 Summary of outstanding actions, including milestones	Medical Expert Pharmacovigilance, if applicable Medical Affairs, if applicable
Part II	**Section I – Evaluation of the need for risk minimisation activities**	**3.1 Summary table of planned actions for each safety concern from RMP section 1.10**	Technical Development Pre-clinical Development Medical Expert Pharmacovigilance Medical Affairs Epidemiology Supply Chain
		3.2 Potential for medication errors	Medical Expert Medical Affairs Regulatory Affairs Pharmacovigilance, if applicable
	Section II – Risk Minimisation Plan		Technical Development Pre-clinical Development Medical Expert Pharmacovigilance Medical Affairs Epidemiology Supply Chain
Summary of the EU Risk Management Plan			Medical Expert Pharmacovigilance, if applicable
Contact person for this EU-RMP			Regulatory Affairs
Annexes			Different departments, depending on the type of data

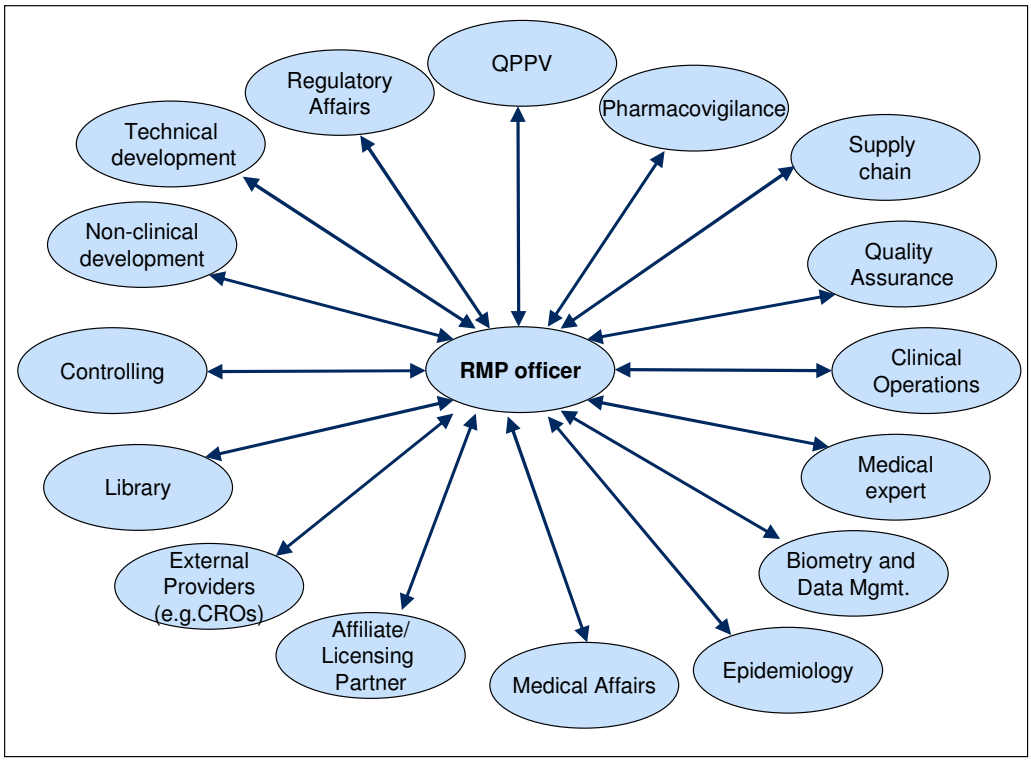
The content of an EU-RMP is explicitly regulated in the template of the "*Guideline on Risk Management Systems for Medicinal Products for Human Use"*.

Table 2 summarises the contribution of the different departments of a pharmaceutical company for each RMP section according to Annex C of the EU-RMP Guideline.

The core role of the RMP officer in the preparation of the EU-RMP is illustrated in Figure 1. With regard to the EU-RMP implementation team, it is not necessary to have a representative from all departments presented in Figure 1, but from departments with major involvement like clinical research

and development, epidemiology, pharmacovigilance, regulatory affairs and medical affairs.

Figure 1: Departments and external parties involved in the RMP development



The core aspect of the preparation of a meaningful and appropriate EU-RMP consists of the effective and aligned cooperation of the departments involved. A thorough planning will lead to an on-time finalisation and submission of the EU-RMP in order to avoid any delay. To coordinate this multifunctional task successfully, an RMP officer should be nominated and provided with adequate authority. Good time management and a well-prepared and sound EU-RMP can lead to a faster assessment by the regulatory authority and potentially will accelerate the overall approval process.

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Unterschrift