1 24 February 2016
2 EMA/838713/2011 Rev 2* Draft for public consultation

3 Guideline on good pharmacovigilance practices (GVP)

4 Module V – Risk management systems (Rev 2)

Date for coming into effect of Revision 1	28 April 2014
Draft Revision 2* finalised by the Agency in collaboration with Member States	16 February 2016
Draft Revision 2 agreed by the European Risk Management Facilitation Group (ERMS FG)	23 February 2016
Draft Revision 2 adopted by Executive Director	24 February 2016
Release for public consultation	29 February 2016
End of consultation (deadline for comments)	31 May 2016
Anticipated date for coming into effect after finalisation	Q3 2016

5

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu

6 * Note: Revision 2 is a major revision with modifications throughout, based on experience gained over
7 the past 3 years and contains the following:

8 – further clarification of what RMPs should focus on in relation to an important identified or
9 important potential risk and missing information;

10 – removal of duplication within GVP Module V;

11 – removal of duplication of information in other guidance documents;

12 – further guidance on the expected changes in the RMP during the life cycle of the product;

13 – updated requirements for different types of initial marketing authorisation applications, with the
14 aim to create risk-proportionate, fit for purpose RMPs.

15 The guidance is updated in parallel to an amended RMP template for initial marketing authorisation
16 application, which undergoes public consultation in parallel.

17 In parallel to this public consultation of GVP Module V Rev 2, the Agency will take into account findings
18 from the pilot phase of publishing RMP summaries for centrally authorised products.

Questions on which the Agency seeks specific feedback by means of the public consultation:

1. The updated risk definitions and guidance on Part II Module SVII of the RMP may lead, in the post-authorisation phase, to a list of safety concerns in the RMP that is a subset of the list of the product safety concerns as defined in the PSUR. What should be the priority of the GVP Module V: a focused RMP list of safety concerns or the full alignment with the PSUR content?
2. Should studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) be included, for information, in the RMP annex 2?
3. Should the additional risk minimisation materials as they were distributed in the Member States be included in the annexes of the RMP (i.e. RMP annex 6 – part B)?
4. Should section V.B.10 be maintained or deleted (i.e. in the light of the RMP terminology described in V.A.1.)?

19

Table of contents

V.A. Introduction

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk balance is judged to be positive for the target population. Generally, a medicinal product will be associated with adverse reactions and these will vary in terms of severity, likelihood of occurrence, effect on individual patients and public health impact. However, not all actual or potential adverse reactions will have been identified at the time when an initial marketing authorisation is granted and some will only be discovered and characterised in the post-authorisation phase. The aim of a risk management plan (RMP) is to address uncertainties regarding the safety profile at different points in a medicinal product's life cycle and to plan risk management activities accordingly. As knowledge regarding a medicinal product's safety profile increases, it is expected the risk management plan will change. To this end, the RMP contains the following:

1. 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');
2. 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');
3. planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 (hereinafter referred to as REG, DIR and IR) include provisions for post-authorisation safety studies and post-authorisation efficacy studies to be a condition of the marketing authorisation in certain circumstances [REG Art 9(4), Art 10a(1), DIR Art 21a, Art 22a(1)] and for these studies to be included in the risk management system [REG 14a, DIR Art 22c, IR Art 30(1)(d)]. The legislation also includes provisions for additional risk minimisation activities to be a condition to the marketing authorisation [REG Art 9(4), DIR Art 21a]. Marketing authorisation applicants are encouraged to plan from very early on in a product's life cycle how they will further characterise and minimise the risks associated with the product in the post-authorisation phase.

Guidance on templates and submission of RMPs is kept up-to-date on the Agency's website[1].

This Module includes the principles of risk minimisation and should be read in conjunction with GVP Module XVI.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

The following articles provide the main references in relation to the legal basis for risk management but additional articles may also be relevant:

- Directive 2001/83/EC Article 8(3)(ia) and (iaa), Article 21a, Article 22a, Article 22c, Article 104, Article 106(c), Article 127a;
- Regulation (EC) No 726/2004 Article 6(1), Article 9(4)(c), (ca), (cb), (cc), Article 10a, Article 14a, Article 26(c);

[1] See www.ema.europa.eu

- Commission Implementing Regulation (EU) No 520/512 Article 30, Article 31, Article 32, Articles 33, Annex 1;
- Regulation (EC) No 1901/2006 Article 34;
- Regulation (EC) No 1394/2007 Article 14.

V.A.1. Terminology

Without prejudice to the terminology provided in GVP Annex I, more focused definitions of (important) identified or potential risks and missing information are developed herein below, to apply in the EU for the purpose of the risk management system, as follows:

Identified risk in the RMP (within this Module referred to as "identified risk")

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.

Potential risk in the RMP (within this Module referred to as "potential risk")

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.

Important identified risk and important potential risk in the RMP (within this Module referred to as "important identified risk and important potential risk", or occasionally "important risk")

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 (see V.B.7.).

Typically, 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.

Missing information in the RMP (within this Module referred to as “missing information”)

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’.

Safety concern in the RMP (within this Module referred to as “safety concern”)

Any of the important identified risks, important potential risks, or missing information included in the RMP.

Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions [DIR Art 1(28b)].

Risk management plan

A detailed description of the risk management system [DIR Art 1(28c)].

Risk minimisation activity (used synonymously with risk minimisation measure)

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.

Where the terms “(important) identified risk”, “(important) potential risk”, “missing information” and “safety concern” are used in other GVP Modules and not in relation to the RMP, the definitions in GVP Annex I apply without the respective focus described above for the EU GVP.

V.B. Structures and processes

V.B.1. Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin. The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a medicinal product’s life cycle. The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data [DIR Art 8(3)].

The RMP is a dynamic document that should be updated throughout the life cycle of the product(s). This includes the addition of safety concerns where required, but also, as the safety profile is further characterised, the removal or reclassification of safety concerns.

The guidance on risk classification in this document may facilitate that during the life cycle of the products the list of safety concerns in the RMP will be reduced (see also V.A.1. and V.B.4.8.):

- 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 characterise 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 minimisation 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 minimisation 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.

V.B.2. Responsibilities for risk management

The principal organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the competent authorities who regulate the medicinal products.

An applicant/marketing authorisation holder is responsible for:

- having an appropriate risk management system in place [DIR 8(3)(iaa); Art 104(3)(c)];
- ensuring that the knowledge and understanding gained regarding the product's safety profile following its use in clinical practice is critically reviewed. The marketing authorisation holder (MAH) should update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products [Dir Art 104(3)(e)], as described below. The critical review of safety profile of the product is a continuous activity and is reflected in data submitted with Periodic Safety Update Reports (PSUR) (see GVP Module VII), where an RMP submission may or may not be warranted. In addition, there are two specific moments when the MAHs are advised to reflect on the need to review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimisation activities: with the 5-year renewal and around the submission of the first PSUR following the (first) renewal (usually 8-9 years following the granting of the marketing authorisation - when the assessment of the generic products for the active substance commences).

V.B.3. Format and contents of the risk management plan (RMP)

The RMP consists of seven parts. Part II of the RMP - Safety specification is subdivided into modules [IR Annex I], so the content can be tailored to the specifics of the medicinal product or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the safety specification of ICH-E2E (see GVP Annex IV). The modular structure aims to facilitate updating of the RMP. In addition, in specific circumstances certain RMP modules may have reduced content requirements (see V.C.2.1.).

The submitted RMP should follow the RMP template in IR Annex I[2]. 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.

An overview of the parts and modules of the RMP is provided below in Table V.1. [IR Annex I]:

Table V.1. Overview of the RMP parts and modules

Part I	Product(s) overview
Part II	Safety specification
Module SI	Epidemiology of the indication(s) and target population(s)
Module SII	Non-clinical part of the safety specification
Module SIII	Clinical trial exposure
Module SIV	Populations not studied in clinical trials
Module SV	Post-authorisation experience
Module SVI	Additional EU requirements for the safety specification
Module SVII	Identified and potential risks
Module SVIII	Summary of the safety concerns
Part III	Pharmacovigilance plan (including post-authorisation safety studies)
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)
Part VI	Summary of the risk management plan
Part VII	Annexes

Information in the RMP should be provided in enough detail whilst avoiding unnecessary text that distracts from the key issues to be considered for risk management of the product. However, the safety specifications in the RMP should not be a duplication of data submitted elsewhere; where applicable, the information in the RMP should provide an integrated overview/discussion focusing on the most important risks that have been identified or are anticipated based on pre-clinical, clinical and post-marketing data presented in other modules of the eCTD. Any data included in the RMP should be consistent with other sections of the dossier. Links to relevant sections of the non-clinical and clinical overviews and summaries should be included in the RMP core document.

For new RMP submissions for nationally authorised products with limited safety data in the dossier, the RMP may contain the relevant safety data and discussion, to support the risk identification.

[2] EMA/465932/2013; available on EMA website http://www.ema.europa.eu.

To aid consistency between the information provided in the eCTD and the RMP, Table V.2. indicates where information from the eCTD is likely to be discussed in the RMP:

Table V.2. Mapping between RMP modules and eCTD

RMP Module	eCTD
Part I Product(s) overview	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5 Clinical overview
Module SII Non-clinical part of the safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary - briefly Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorisation experience	Module 2.5 Clinical overview – briefly
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance plan (including post-authorisation safety studies)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post-authorisation efficacy studies	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Module 2.5 Clinical overview Module 2.7 Clinical summary

Literature referenced in the RMP should be included in RMP annex 7. This should be in the format of links if already included elsewhere in eCTD (see V.B.9.).

The description of the parts and modules of an RMP provides guidance on the main topics to be covered within each specific area. However, some sections may not be relevant to all medicinal products and there may be additional topics that need to be included but are not mentioned in this guidance. The RMP is part of the scientific dossier of a product and as such should be science based and not promotional.

V.B.3.1. RMP part I "Product(s) overview"

This should provide the administrative information on the RMP and an overview of the product(s). The information presented should be current and accurate in relation to the ongoing application as it is anticipated to appear in the marketing authorisation. When applicable, the changes from an indication already approved should be highlighted in the document.

The information should include:

Active substance information:

- active substance(s);

- pharmacotherapeutic group(s) (ATC code);
- name of marketing authorisation holder or applicant;
- medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

- data lock point of the current RMP;
- date submitted and the version number of the RMP;
- list of all parts and modules. For RMP updates, modules version number and date of approval (opinion date) should be tabulated in this section. High level comment on the rationale for creating the update should be included for significant changes to each module;
- authorisation procedure (central, mutual recognition, decentralised, national);
- invented name(s) in the European Economic Area (EEA);
- brief description of the product including:
  - chemical class;
  - summary of mode of action;
  - important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- eCTD link to the currently approved PI;
- indications;
- dosage (summary information – only related to main population; not a duplication of SmPC section 4.2);
- pharmaceutical forms and strengths;
- whether the product is subject to additional monitoring in the EU (at initial marketing authorisation application conclusion or with RMP updates).

The QPPV (see GVP Module I) signature is not required for RMP versions submitted for assessment; this can be included in the closing sequence in the finalised approved version of the RMP.

V.B.4. RMP part II "Safety specification"

The purpose of the safety specification is to provide an adequate discussion on the safety profile of the medicinal product(s), with focus on those aspects that need further risk management activities. It should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information. It should also address the populations potentially at risk (where the product is likely to be used i.e. both as authorised and off-label use), and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk balance during the post-authorisation period. The safety specification forms the basis of the pharmacovigilance plan and the risk minimisation plan.

The safety specification consists of eight RMP modules of which RMP modules SI-SV, SVII and SVIII correspond to safety specification headings in ICH-E2E. RMP module SVI includes additional elements required to be submitted in the EU.

Although the elements outlined below serve as a guide only, it is recommended that applicants/marketing authorisation holders follow the structure provided when compiling the safety specification. Where needed for risk management planning purposes, the safety specification may include additional elements such as:

- the disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches);
- innovative pharmaceutical forms;
- use with a medical device and risk associated with the medical device;
- environmental impact;
- exceptionally, quality aspects relevant in relation to the safety of the product and not adequately addressed at time of marketing authorisation.

Details of specific requirements for initial marketing authorisation applications are included in V.C.1.1..

V.B.4.1 General considerations for generic products and advanced therapy medicinal products

V.B.4.1.1. Generics

For generic medicinal products the expectation is that the safety specification is the same as that of the reference product or of other generic products for which an RMP is in place. If discrepancies exist between approved RMPs for such products, then the applicant is expected to propose and justify the most appropriate safety specification for their product. RMP summaries for most recently approved centrally authorised medicinal products (CAPs) are published on EMA website[3]. The CMDh has published the summary of safety concerns for selected medicinal products for which an RMP is in place, on the CMDh website[4]. Exceptionally, the applicant for a new generic medicinal product may add or remove safety concerns compared with the safety profile of the reference product if this is appropriately justified (for example, when there is a more up to date understanding of the current safety profile or when there are differences in product characteristics compared with the reference product, e.g. there is a risk associated with an excipient present only in some of the products containing the same active substance).

V.B.4.1.2. Advanced therapy medicinal products

Under Regulation (EC) No 1394/2007 on advanced therapy medicinal products, certain products for human medicinal use are categorised within the EU as advanced therapy medicinal products (ATMPs). These products are fully defined in the above Regulation but broadly comprise:

- gene therapy medicinal products;
- somatic cell therapy medicinal products;
- tissue engineered products.

Because of the nature of these products, risks may occur that are not normally a consideration with other medicinal products including risks to living donors, risks of germ line transformation and

[3] See http://www.ema.europa.eu.
[4] See http://www.hma.eu/464.html.

transmission of vectors. This needs to be taken into consideration when developing the safety specification for ATMPs.

V.B.4.2. RMP module SI "Epidemiology of the indication(s) and target population(s)"

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. Differences in the epidemiology in different regions should be discussed where it varies across regions.

This section should also describe the relevant adverse events to be anticipated in the target population, their frequency and characteristics. The text should help anticipate and interpret any potential signals and help identify opportunities for risk minimisation. The text should be kept concise and not be promotional.

For guidance on when information should be provided on co-morbidities in the target population, please consider the following examples:

- if the target population for a medicinal product is men with prostate cancer, the target population is likely to be men over the age of 50 years. They also have an increased risk for myocardial infarction. To identify whether such a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not taking the medicinal product. Estimation of the risk in the target population, as compared with the same age/gender group in the general population may be particularly important if the disease itself increases the risk.
- if a product is associated with an increased risk of congenital malformations, then it will be useful to have insight into the potential frequency and duration of use in women of childbearing potential, to help decide on the potential need for and the design of effective risk minimisation activities.

V.B.4.3. RMP 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.

What constitutes an important safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Normally significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans should be discussed. Also, quality aspects if relevant to safety (e.g. important information on the active substance or its impurities, e.g. genotoxic impurities) should be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population discussed. Where the non-clinical

safety finding could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII. Where the non-clinical safety finding is not considered relevant for human beings, provision of a brief explanation is required.

If, based on the assessment of the non-clinical or clinical data, additional non-clinical studies are considered warranted, this should be briefly discussed here.

Final conclusions on this section should be aligned with content of module SVII and any safety concerns should be carried forward to module SVIII.

V.B.4.4. RMP module SIII "Clinical trial exposure"

In this RMP module, in order to assess the limitations of the human safety database, 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. This should be stratified for relevant categories; stratifications would normally include:

- age and gender;
- indication;
- dose;
- other stratifications should be provided where this adds meaningful information for risk management planning purposes.

Paediatric data should be divided by age categories (e.g. ICH-E11[5]); similarly the data on older people should be stratified into age categories reflecting the target population (e.g. 65-74, 75-84 and 85 years and above). For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate.

Unless clearly relevant and duly justified, data should not be presented by individual trial but instead, they should be pooled. Totals should be provided for each table/graph as appropriate. Where patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/gender/ethnic origin tables. Reasons for differences in the total numbers of patients between tables should be explained.

When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being pooled across all indications.

V.B.4.5. RMP module SIV "Populations not studied in clinical trials"

Populations that are considered under missing information should be described in this RMP module.

When exclusion criteria from the clinical trial development programme are not proposed as contraindications for the medicinal product, then RMP module SIV should also include a discussion on the relevant subpopulations, including whether or not any use in populations excluded from the clinical

[5] See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590.

trials (e.g. women of childbearing potential, older people) might be associated with a different list of safety concerns and should be included as missing information in the RMP.

In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria.

The exposure or the lack of, in special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised, and different ethnic origins) should be provided where available and as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the type of genetic polymorphism.

V.B.4.6. RMP module SV "Post-authorisation experience"

If post-marketing data are available from an authorised product from the same MAH containing the same active substance or from post-authorisation experience in other regions outside EU, where the product is already authorised, the data should be discussed in this RMP module.

It should only provide an overview of experience in the post-authorisation phase that is helpful for risk management planning purposes. It is not the intention to duplicate information from the PSUR. High-level information on the number and characteristics of patients exposed post-authorisation should be included, when available.

Additionally, a discussion on how the medicinal product is being used in practice and on labelled and off-label use, including use in the special populations mentioned in RMP module SIV, can also be included when relevant for the risk identification discussion in module SVII.

Where appropriate and relevant for the discussion in SVII, data on unauthorised use in markets outside the EU should also be summarised and the implications for the authorisation in the EU should be discussed.

V.B.4.7. RMP 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 (see also V.B.7.).

V.B.4.8. RMP module SVII "Identified and potential risks"

This RMP module should provide a focussed 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, for example in cases where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from

overdose has occurred during clinical trials this should be explicitly mentioned and, where relevant, overdose should be included as a safety concern in RMP module SVIII and appropriate risk minimisation proposed in RMP part V;

- *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. Further guidance on medication errors is provided in Good practice guide on recording, coding, reporting and assessment of medication errors[6].including in "Annex 2 - Design features which should be considered to reduce the risk of medication error" an extensive list of potential medication errors and the consequence to the patients. Adverse reactions related to medication errors in the post marketing period should be discussed in the updated RMP and ways of limiting the errors proposed;

- *potential for transmission of infectious agents*, for instance because of the nature of the manufacturing process or the materials involved. For live attenuated vaccines any potential for transmission of mutated live vaccine virus, and the potential of causing the disease in immunocompromised contacts of the vaccine should be discussed;

- *potential for off-label use* should be discussed with a focus on any anticipated differences in safety concerns between the target and the off-label population. Off-label use is particularly relevant in situations where the medicinal product must not be given for known safety reasons. The potential for use in other disease areas should also be considered where this is suspected to be related to a different safety profile. In such cases, potential or identified risks arising from the off-label use of the product should be considered for inclusion in the safety specifications;

- 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. The evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks discussed for different indications and populations. Important (potential) risks following clinically important interactions should be considered for inclusion as a safety concern;

- risks in pregnant and lactating women, e.g. teratogenic risk - direct or through exposure to semen: contraception recommendations can be considered as risk minimisation measures. Further guidance on risk management in case of exposure of the embryo / foetus to teratogenic agents can be found in the GVP P.III.;

- effect on fertility - appropriate risk minimisation measures should be considered, e.g. routine risk communication and/or additional activities recommending fertility preservation: sperm cryopreservation in men and embryo and oocyte cryopreservation in women.

[6] EMA/762563/2014; available on EMA website http://www.ema.europa.eu

For RMPs of advanced therapy medicinal products (ATMPs), the applicants should also consider the following possible risks in drafting the safety specifications (see Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products[7]):

- risks to living donors, for instance:
  - risks to living donors related to their conditioning prior to procurement (e.g. immunosuppression, cytotoxic agents, growth factors);
  - risks to living donors related to surgical/medical procedures used during or following procurement, irrespective of whether the tissue was collected or not;
- risks to patients related to quality characteristics of the product, in particular:
  - species of origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing, and the safety testing performed;
  - characteristics of vectors for gene therapy medicinal products;
  - biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
  - quality assurance and characteristics of the finished product in terms of defined composition, stability, biological activity, and purity with reference to non-physiologic proteins and fragments thereof;
  - risk related to transmissible diseases (e.g. viral, bacterial, parasitical infections and infestations, but also malignant disease);
- risks to patients related to the storage and distribution of the product, for instance:
  - risks related to preservation, freezing and thawing;
  - risks of breaking the cold chain or other type of controlled temperature conditions;
  - risks related to stability of the product;
- risks to patients related to administration procedures, for instance:
  - biologically active substances used in preparation of the product prior to administration (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
  - risks related to conditioning of the patient;
  - risks of related medical or surgical procedures (e.g. anaesthesia, infusion, transfusion, implantation, transplantation or other application method);
  - risks related to clinical follow-up (e.g. immunosuppression as co-medication or as necessary for treatment of complications, diagnostic procedures, hospitalisation);
  - risks related to mistakes or violations of the standard procedures for administration of the product (e.g. different administration procedures used by different healthcare establishments/healthcare professionals resulting in differing outcomes);

[7] EMEA/149995/2008; available on EMA website http://www.ema.europa.eu

- risks related to interaction of the product and the patient, for instance:
  - unwanted immunogenicity and its consequences (including e.g. anaphylaxis, graft versus host disease, graft rejection, hypersensitivity reactions, immune deficiencies);
  - risks related to both intended and unintended genetic modification of the patient's cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy);
  - early and late consequences of homing, grafting, differentiation, migration and proliferation;
  - risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene, altered expression of the host's genes);
- risks related to scaffolds, matrices and biomaterials (e.g. biodegradation, mechanical factors);
- risks related to persistence of the product in the patient:
  - availability of rescue procedures or antidotes and their risks;
  - late complications, particularly malignancies and auto-immunity;
  - considerations on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the respective disease on the product, or *vice versa* impact of the product on those other therapies (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction);
- risks related to re-administration, for instance:
  - immune reactions - anaphylaxis, neutralising antibodies;
  - risks related to repeated surgical or administration procedures;
- risks to close contacts, for instance:
  - based on the environmental risk assessment, virus shedding and its consequences;
- specific parent-child risks, for instance:
  - risk of germ line integration of transgene, or other genetic transformation of the germ line;
  - foetal transmission (of e.g. vectors, biologically active substances, cells, infectious agents);
  - trans-mammary exposure of children in breast-feeding women (to e.g. vectors, biologically active substances, cells, infectious agents).

V.B.4.8.1. RMP module SVII section "Identification of safety concerns in the initial RMP submission"

This RMP section should contain the initial identification of safety concerns and is expected to be populated for RMPs submitted with the initial marketing authorisation (MA) application, or with a new RMP submitted post-authorisation (at the competent authority's request or without request).

V.B.4.8.1.a. RMP module SVII sections "Risk considered important for inclusion in the safety specification" and "Risk not considered important for inclusion in the safety specification"

In this RMP section, for each risk, the following information should be summarised and discussed:

- [for risks taken forward 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.

V.B.4.8.2. RMP module SVII section "Identification of safety concerns with a submission of an updated RMP"

For post-authorisation RMP updates, newly identified risks not considered important or missing information, for which new significant emerging data is available since the last submission of the RMP, should be discussed in this RMP section.

V.B.4.8.2.a. RMP module SVII section "Newly identified risks of the product"

Data presented in this RMP section shall follow same requirements as detailed in V.B.4.8.1.1..

V.B.4.8.2.b. Justification on the safety concerns re-classification (deletion, addition, downgrade and/or upgrade)

When an important risk or missing information is re-classified or removed, a justification should be provided in this RMP section.

V.B.4.8.3. RMP module SVII section "Details of important identified and potential risks, and missing information"

For RMPs covering multiple products where there may be significant differences in the identified and potential risks or missing information for different products (e.g. fixed dose combination products), it is appropriate to make it clear which safety concerns relate to which product.

This RMP section applies to all stages of the product's life cycle.

Presentation of important identified and important potential risks data:

- 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 minimised by routine or additional risk minimisation activities other than general awareness using the PI; 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).

Presentation of missing information data:

- 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 characterisation;
- 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 characterised risk and the product is confirmed to be strong (i.e. worst case scenario).

V.B.4.9. RMP module SVIII "Summary of the safety concerns"

In this RMP module, a list of safety concerns should be provided with the following categories:

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

V.B.5. RMP part III "Pharmacovigilance plan"

The purpose of the pharmacovigilance plan in part III of the RMP is to present an overview and discuss how the applicant/marketing authorisation holder plans to further characterise the risks identified in the safety specification. It provides a structured plan for:

- the investigation of whether a potential risk is real or not;
- further characterisation of safety concerns including severity, frequency, and risk factors;
- how missing information will be sought;
- measuring the effectiveness of risk minimisation 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. Early discussions between competent authorities and the applicant/marketing authorisation holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed and consequently milestones should be agreed.

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

V.B.5.1. RMP part III section "Routine pharmacovigilance activities"

Routine pharmacovigilance is the primary/minimum set of activities required for all medicinal products as per the obligations set out in Directive 2001/83/EC and Regulation (EC) No 726/2004. Signal detection, which is part of routine pharmacovigilance, is an important element in identifying new risks for all products. The descriptions of these activities in the pharmacovigilance system master file (see GVP Module II) are not required to be repeated in the RMP.

The Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Medicinal Products for Human Use (CHMP) or the Coordination Group for Mutual recognition and Decentralised Procedures – Human (CMDh) may make recommendations for specific activities related to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine pharmacovigilance (see GVP Module I). If these recommendations include recording of tests (including in a structured format) that would form part of normal clinical practice for a patient experiencing the adverse reaction, then this requirement would still be considered routine. The routine pharmacovigilance section of the pharmacovigilance plan should be used in these circumstances to explain how the applicant will modify its routine pharmacovigilance activities to fulfil any special PRAC, CHMP or CMDh recommendations on routine pharmacovigilance.

However, if the recommendation includes the submission of tissue or blood samples to a specific laboratory (e.g. for antibody testing) that is outside "normal" clinical practice, then this would constitute an additional pharmacovigilance activity.

This RMP section should describe only the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

V.B.5.1.1. Specific adverse reaction follow-up questionnaires

Where an applicant/marketing authorisation holder is requested, or plans, to use specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest, the use of these materials should be described in the routine pharmacovigilance activities section and copies of these forms should be provided in RMP annex 4.

Without prejudice to the originality of the format of the questionnaire(s), it is in the interest of public health that questionnaire(s) used by different applicants/marketing authorisation holders for the same adverse event should be kept as similar as possible, in order to deliver a consistent message and decrease the burden on healthcare professionals. Therefore, marketing authorisation holders are strongly encouraged to share the content of their questionnaire(s) upon request from other marketing authorisation holders.

V.B.5.1.2. Other forms of routine pharmacovigilance activities

Other forms of routine pharmacovigilance activities to be described in this section include e.g. enhanced passive surveillance, requested observed versus expected analyses in the PSUR, requested re-evaluation of risks in the PSURs, cumulative reviews of adverse events of interest.

V.B.5.2. RMP part III section "Additional pharmacovigilance activities"

For each safety concern, the applicant/marketing authorisation holder should list in this RMP section their planned additional pharmacovigilance activities for that concern, detailing what information is expected to be collected that can lead to a more informed consideration of the benefit-risk balance.

Additional pharmacovigilance activities are pharmacovigilance activities that are not considered routine. They may be non-clinical studies, clinical trials or non-interventional studies. Examples include long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterisation of the long-term safety of the medicinal product. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a competent authority should be considered.

Studies in the pharmacovigilance plan aim to identify and characterise risks, to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimisation activities. They should relate to the safety concerns identified in the safety specification, be feasible and not be promotional.

Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place, recommendations in the GVP Module VIII. MAAs and MAHs may submit to EMA or national competent authorities PASS protocols for Scientific Advice.

Until completion of the study and submission to the competent authorities of the final study report, protocols for studies in the pharmacovigilance plan should be provided in RMP annex 3. RMP annex 3 – part A should contain protocols submitted for assessment, when the protocol submission has been

requested by the competent authority; RMP annex 3 – part B should contain protocols that have been agreed with competent authorities and are being submitted with the RMP for amendment, when the protocol submission has been requested by the competent authority; RMP annex 3 – part C should contain protocols already approved and other category 3 studies protocols, submitted for information only (see V.B.10.).

Milestones, including a time point for the final study report submission to the competent authority, should be included.

V.B.5.3. RMP part III section "Summary table of additional pharmacovigilance activities"

This RMP section outlines the pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions of the marketing authorisation, either because they are key to the benefit-risk profile of the product (category 1 studies in the pharmacovigilance plan), or because they are specific obligations in the context of a conditional marketing authorisation (MA) or a MA under exceptional circumstances (category 2 studies in the pharmacovigilance plan). If the condition or the specific obligation is a non-interventional PASS, it will be subject to the supervision set out in Art 107 (m)-(q) of Directive 2001/83/EC and the format and content of such non-interventional PASS as described in IR Annex III (see GVP Module VIII).

Other studies required in the pharmacovigilance plan are legally enforceable (category 3 studies in the pharmacovigilance plan). The summary table of the pharmacovigilance plan should provide clarity to all stakeholders as to which category an activity in the pharmacovigilance plan falls under (see Table V.3.).

Studies required in jurisdictions outside the EU should not be included in the RMP unless they are also imposed as a condition to the MA or as a specific obligation, or required by the Agency or a national competent authority. Studies not required by the EU or national competent authority should not be included in the pharmacovigilance plan in the RMP. This is without prejudice to safety concerns arising from any such studies, which should be reported as per the applicable legislation.

775 **Table V.3.** Attributes of additional pharmacovigilance activities

	Type of activity	In annex II of MA (CAPs only)	Study category (PhV Plan)	Status	Supervised under	
					Article 107m	Article 107 n-q
Imposed PASS	"Interventional"*	☑	1	Mandatory and subject to penalties		
	Non-interventional	☑			☑	☑
Specific obligation	"Interventional"*	☑	2	Mandatory and subject to penalties		
	Non-interventional	☑			☑	☑
Required	"Interventional"*		3	Legally enforceable		
	Non-interventional				☑	

776 *Clinical interventional studies are subject to the requirements of Directive 2001/20/EC. Non-clinical interventional
777 studies are subject to the legal and ethical requirements related to the protection of laboratory animals, and Good
778 Laboratory Practice as appropriate.

779 For generic products, the pharmacovigilance plan will reflect the outstanding needs for
780 pharmacovigilance investigations at the time of the approval. In some cases, ongoing or planned PASS
781 for the originator would also be required to be conducted for the generic products (e.g. registries may
782 need to be in place to include most/all patients treated with the medicine, be it generic or originator
783 products). Where applicable, the MAHs are encouraged to set up joint PASS, for instance in the case of
784 registries or when a referral has resulted in an imposed PASS for all authorised medicinal products
785 containing a named substance in a specified indication.

786 *V.B.6. RMP part IV "Plans for post-authorisation efficacy studies"*

787 This RMP part should include a list of post-authorisation efficacy studies (PAES) imposed as conditions
788 of the marketing authorisation or when included as specific obligations in the context of a conditional
789 MA or a MA under exceptional circumstances. If no such studies are required, RMP Part IV may be left
790 empty where not applicable.

791 For most medicines there will be no need for post-authorisation efficacy studies. However, there may
792 be circumstances where efficacy data in the authorised indications need to be obtained in the post-
793 authorisation phase, e.g. where there are concerns about efficacy that can only be resolved after the
794 product has been marketed, or when new knowledge about the disease or the clinical methodology
795 used to investigate efficacy indicate that previous efficacy evaluations may need significant revision.
796 PAES may be requested from marketing authorisation holders in accordance with REG Art 9(4)(cc) and
797 Art 10a(1)(b) and DIR Art 21a(f) and Art 22a(1) , as well as Commission Delegated Regulation (EU) No
798 357/2014. Post-authorisation efficacy studies can also be imposed as specific obligations for a
799 marketing authorisation in accordance with REG Art 14(7) or Art 14(8) or DIR Art 22.

800 Regulation (EC) No 1901/2006 on medicinal products for paediatric use) and Regulation (EC) No
801 1394/2007 on advanced therapy medicinal products specify the potential need for long-term follow-up
802 of efficacy as part of post-authorisation surveillance for certain medicinal products, namely:

803 • applications for a marketing authorisation that include a paediatric indication;

- applications to add a paediatric indication to an existing marketing authorisation;
- application for a paediatric use marketing authorisation;
- advanced therapy medicinal products.

The request for a PAES refers solely to the current indication(s) and not to studies investigating additional indications.

V.B.7. RMP part V "Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)"

This part V of the RMP should provide details of the risk minimisation measures which will be taken to reduce the risks associated with respective safety concerns. Consideration must be given to the risk proportionality of the risk minimisation activity proposed, the feasibility of implementing any additional risk minimisation activity in all Member States, whether the proposed measures are necessary for the safe and effective use of the product in all patients, and the possibility to adapt distribution modalities for such risk minimisation activities so as best to suit different healthcare settings.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product, for example for products with different legal status for the supply of medicinal products to patients (e.g. prescription-only) medicinal products where the indications lie in different medical specialities and have different safety concerns associated, or active substances where risks differ according to the target population.

The need for continuing risk minimisation measures should be reviewed at regular intervals and the effectiveness of risk minimisation activities assessed (see V.B.7.). Guidance on additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures is provided in GVP Module XVI.

Routine risk minimisation activities

Routine risk minimisation activities are those which apply to every medicinal product. These relate to:

- the summary of product characteristics;
- the labelling (e.g. on inner and outer carton);
- the package leaflet;
- the pack size(s);
- the legal status of the product.

Even the formulation itself may play an important role in minimising the risk of the product.

Summary of product characteristics (SmPC) and package leaflet (PL)

The summary of product characteristics and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal product. The Guideline on Summary of Product Characteristics provides guidance on how information should be presented.

Both materials provide routine risk minimisation recommendations; however, there are two types of messages the SmPC and PL can provide:

- **routine risk communication messages**: usually found in section 4.8 of the SmPC or section 4 of the PL; these messages communicate to healthcare professionals and patients the side effects of the medicinal product, so that an informed decision on the treatment can be made;
- **routine risk minimisation activities beyond routine risk communication:** usually found in sections 4.2 and 4.4 of the SmPC but can also be found in sections 4.6 and 4.5 and accordingly sections 2 and 3 of the PL; warning and precaution messages and recommendations in the SmPC will include information on minimising the risk of the product by e.g.:
  - performing a test before the start of treatment;
  - monitoring of laboratory parameters during treatment
  - monitoring for new signs and symptoms
  - adjusting the dose or stopping the treatment when adverse events are observed or laboratory parameters change
  - performing a wash-out procedure after treatment interruption
  - providing contraception recommendations
  - prohibiting the use of other medicines while taking the product
  - treating or preventing the risk factors that may lead to an adverse event of the product
  - providing long-term clinical follow-up to identify in early stages delayed adverse events.

Pack size

Since every pack size is specifically authorised for a medicinal product, planning the number of "dosage units" within each pack and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of "dosage units" should mean that patients will need to see a healthcare professional at defined intervals, thus increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.

A small pack size can also be useful, especially if overdose or diversion are thought to be major risks.

Legal status

Controlling the conditions under which a medicinal product may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal product may be prescribed or administered.

The marketing authorisation must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which a medicinal product may be made available to patients. This is commonly referred to as the "legal status" of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medicinal prescription [DIR Art 71(1)]. It may also restrict where the medicinal product can be administered (e.g. in a hospital) or by whom it may be prescribed (e.g. specialist).

For medicinal products only available on prescription, additional conditions may be imposed by classifying them into those available only upon either a restricted medical prescription, or upon a special medical prescription.

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicine can be given or used. According to EU legislation, when considering classification of a medicinal product as subject to restricted medical prescription, the following factors shall be taken into account [DIR Art 71(3)]:

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
- the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or
- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

Special medical prescription

For classification as 'subject to special medical prescription', the following factors shall be taken into account [DIR Art 71(2)]:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971;
- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or
- the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.

Categorisation at Member State level

There is the possibility of implementing sub-categories at Member State level, which permits the Member States to tailor the above-mentioned classifications to their national situation. The definitions and therefore also the implementation vary in those Member States where the sub-categories exist.

Additional risk minimisation activities

Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided. Any communication material should be clearly focused on the risk minimisation goals, and should not be combined with promotional material for marketing campaigns. The need for continuing with such measures should be periodically revisited.

Marketing authorisation applicants/holders are encouraged to discuss risk minimisation plans with the competent authorities as early as is feasible e.g. when it is likely that specific risk minimisation activities will need to be adapted to the different healthcare systems in place in the different Member States. When drafting the Risk Minimisation Plan, the applicants are advised to consult patients and healthcare professionals and discuss the proposed risk minimisation activities, as appropriate and when possible.

Where relevant, details of additional risk minimisation activities should be provided in RMP Annex 6 – Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III.

The final version of the risk minimisation materials (educational materials, patient alert cards etc.) and the distribution plan will need to be approved by the national competent authority for the territory in which it will be used. Patient alert cards for centrally authorised products are part of the QRD and they are therefore agreed and translated centrally.

Without prejudice to the originality of the format of the educational materials, it is in the interest of public health that educational materials used by different applicants/marketing authorisation holders for the same active substance be kept as similar as possible, in order to deliver a consistent message and avoid confusion in the target audience (see GVP Module XVI Addendum I – Educational materials).

For medicinal products approved non-centrally, in situations where the need for additional risk minimisation may vary across member states, the RMP can reflect that the need for (and content of) additional risk minimisation can be agreed at a national level.

Further guidance on additional risk minimisation measures is provided in GVP Module XVI.

Evaluation of the effectiveness of risk minimisation activities

The success of risk minimisation activities needs to be evaluated throughout the life cycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall benefit-risk balance is optimised.

When the RMP is updated, the risk minimisation plan should include a discussion of the impact of additional risk minimisation activities. Where relevant, such information may be presented by region. A discussion on the results of any formal assessment(s) of additional risk minimisation activities should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then consideration should be given to alternative activities. The marketing authorisation holder should comment on whether additional or different risk minimisation activities are needed for each safety concern or whether in their view the (additional) risk minimisation measures may be removed (e.g. when risk minimisation measures have become part of standard clinical practice).

If a study to evaluate the effectiveness of risk minimisation activities is required or imposed by the competent authority, the study should be included in the pharmacovigilance plan, part III of the RMP.

Guidance on monitoring the effectiveness of risk minimisation activities is included in the GVP Module XVI.

V.B.7.1. RMP part V section "Risk minimisation plan"

In the RMP section on the risk minimisation plan, for each safety concern in the safety specification, the following information should be provided:

- routine risk minimisation activities, including details of whether only inclusion in the SmPC and PL is foreseen or any other routine risk minimisation activities are proposed;

- additional risk minimisation activities (if any), individual objectives and justification of why needed; for each additional risk minimisation activity, the following information on measuring their effectiveness should be presented:
  - how the effectiveness of each (or all) of the risk minimisation activities will be evaluated in terms of attainment of their stated objectives;
  - what the target is for the additional risk minimisation measures, i.e. what are the criteria for judging success;
  - milestones for reporting on the effectiveness of the additional risk minimisation measures as well as milestones for evaluating the need to maintain the activities (e.g. at renewal and thereafter with the PSURs).

V.B.7.2. RMP part V section "Summary of risk minimisation measures"

A table listing the routine and additional risk minimisation activities by safety concern should be provided in this RMP section (e.g. the SmPC section number where the risk appears in the SmPC, the list of educational materials). A further summary of pharmacovigilance activities should be included, as described in the EMA Guidance on Format of the Risk Management Plan in the EU [8].

V.B.8. RMP part VI "Summary of the risk management plan"

A summary of the RMP for each authorised medicinal product shall be made publicly available and shall include the key elements of the risk management plan [REG Art 23(3), Art 26(1)(c), DIR Art 106(c), IR Art 31(2)].

Part VI of the RMP shall be provided by the marketing authorisation applicant/holder for medicinal products which have an RMP, regardless of whether they are centrally or nationally authorised in the EU. Based on the information contained in part VI of the RMP, for centrally authorised products, the Agency should publish the RMP summary on the EMA website at the time of the European Commission Decision together with the other documents of the European Public Assessment Report (EPAR) of that medicine. For nationally authorised products, a summary of the RMPshould be published on the national competent authorities' websites.

Where an RMP concerns more than one medicinal product, a separate public RMP summary shall be provided for each medicinal product [IR Art 31(2)].

The RMP summary should be updated when important changes are introduced into the full RMP. Changes should be considered important if they relate to the following:

- new important risks or important changes to an important risk (or removal of a safety concern that is no longer considered important);
- inclusion or removal of additional risk minimisation measures;
- major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

[8] EMA/465932/2013; available on EMA website http://www.ema.europa.eu

The audience of RMP summaries is very broad. To ensure that the summary can satisfy the different needs, it should be written and presented clearly, using a plain-language approach[9]. However, this does not mean that technical terms should be avoided. The document should clearly explain its purpose and how it relates to other information, in particular the product information (i.e. the SmPC, the PL and the labelling).

The summary of the RMP part VI should be consistent with the information presented in RMP part II modules SVII, SVIII and RMP parts III, IV and V. It should contain the following information:

- the medicine and what it is used for;
- summary of safety concerns and missing information;
- routine and additional risk minimisation measures;
- additional pharmacovigilance activities.

V.B.9. RMP part VII "Annexes to the risk management plan"

The RMP should contain the annexes listed below (if applicable). If the RMP applies to more than one medicinal product, usually it would be expected that the annexes will be relevant for all products. Particular aspects not applicable to all medicinal products in the RMP should be highlighted (e.g. a follow-up form in annex 4 might only be applicable to the products containing the active substance that is causally linked to the event; educational material in annex 6 might only be applicable to the RMP.

V.B.9.1. RMP annex 1

Annex 1 of the RMP is the structured electronic representation of the EU Risk Management Plan. It is not required to be submitted in eCTD, the electronic file should be submitted in accordance to V.C.2.. and the guidance on EudraVigilance website[10].

V.B.9.2. RMP annex 2: Tabulated summary of on-going and completed pharmacoepidemiological study programme

This annex should include a tabulation of studies included in the pharmacovigilance plan (current or in previous RMP versions; category 1, 2 and 3 studies), as follows:

- ongoing studies, including objectives, safety concern addressed, and the planned dates of submission of intermediate and final results;
- completed studies, including objectives, safety concern addressed, and the date of submission of results to the competent authorities (effective, planned, or state the reason for not submitting the results).

Studies conducted by the MAH but neither required nor imposed by the competent authority (previously classified as category 4 studies) can also be included for information in annex 2.

[9] Plain-language approach includes organising information logically (and giving priority to action points), breaking information into digestible chunks, and using layout that improves readability of a document. http://www.plainenglish.co.uk/campaigning/past-campaigns/legal/drafting-in-plain-english.html (Office of Disease Prevention and Health Promotion. *Plain language: a promising strategy for clearly communicating health information and improving health literacy*. US Department of Health and Human Services, Rockville, http://health.gov/communication/literacy/plainlanguage/IssueBrief.pdf [Accessed 1 Sep 2015])

[10] See http://eudravigilance.ema.europa.eu/human/EURiskManagementPlans.asp

V.B.9.3. RMP annex 3: Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 3 should not include protocols of studies not imposed nor requested by the competent authority (previously classified as category 4 studies). This annex may include the links to other modules of the eCTD dossier where the protocols are included, instead of the full protocol documents.

V.B.9.3.1. RMP annex 3 – part A: Protocols of proposed studies, submitted for regulatory review with this updated version of the RMP

This part A of RMP annex 3 should include the protocols that are proposed for assessment within the same procedure the RMP has been submitted in. This part should be completed only when the study protocol has been requested to be submitted within the RMP for review by the competent authority;; alternatively the protocol might be reviewed in a stand-alone procedure before its integration in the RMP (annex 3 –part C) once agreed. The regulatory pathway is to be agreed with the competent authority.

V.B.9.3.2. RMP annex 3 – part B: Updates of previously approved protocols, submitted for regulatory review with this updated version of the RMP

This part B of RMP annex 3 should be completed only when the study protocol update has been requested to be submitted within the RMP for review by the competent authority, alternatively the protocol might be reviewed in a stand-alone procedure before its integration in the RMP once agreed. The regulatory pathway is to be agreed with the competent authority.

Once approved, protocols from parts A or B should be moved to part C.

V.B.9.3.3. RMP annex 3 – part C

Previously agreed protocols for on-going studies and protocols not reviewed by the competent authority should be included in this part C of RMP annex 3, as follows:

- the full protocols that have been previously assessed by the competent authority and agreed (i.e. no protocol resubmission was requested). The protocols should be accompanied by the name of the procedure when the protocol was approved and date of the outcome. This may include the links to other modules of the eCTD dossier where the protocols have been previously submitted, instead of the full protocol documents.
- the protocols of other category 3 studies, protocols that were not requested to be reviewed by the competent authorities, and are submitted by the MAH for information only.

Protocols of completed studies should be removed from this annex once the final study reports are submitted to the competent authority for assessment.

V.B.9.4. RMP annex 4: Specific adverse event follow-up forms

This annex should include all follow-up forms used by the MAH to collect additional data on specific safety concerns. The usage of follow-up forms included in this annex should be detailed in the pharmacovigilance plan in the RMP, as routine pharmacovigilance activities.

The forms that should be included in this annex are sometimes known as “event follow-up questionnaire”, “adverse event data capture/collection aid” or “adverse reaction follow-up form”.

V.B.9.5. RMP annex 5: Protocols for proposed and on-going studies in RMP part IV

This annex should include links to other parts of the eCTD dossier, where the efficacy study protocols are already included, if such studies were required.

V.B.9.6. RMP annex 6: Details of proposed additional risk minimisation activities

If applicable:

V.B.9.6.1. RMP annex 6 – part A

It should include the proposed draft (and approved, if applicable) key messages of the additional risk minimisation activities (e.g. key messages of the educational materials).

V.B.9.6.2. RMP annex 6 – part B

Should include, for information only, the additional risk minimisation materials as they were distributed in the Member States. Materials included in this annex are not assessed and are not considered endorsed as part of the RMP assessment. The content and distribution plan of the additional risk minimisation activities included in the RMP will only be assessed and agreed at national level (e.g. educational materials messages, brevity, target audience; paper brochure, electronic document; distribution: by MAH representatives, on national competent authority website, with each pack of the product).

V.B.9.7. RMP annex 7: Other supporting data (including referenced material)

When applicable, to avoid duplication of the materials presented as references, this annex should include eCTD links to other documents included in other modules of the dossier.

V.B.10. The relationship between the risk management plan and the periodic safety update report

The primary post-authorisation pharmacovigilance documents for safety surveillance are the RMP and the periodic safety update report (PSUR). Although there is some overlap between the documents, the main objectives of the two are different and the situations when they are required are not always the same. Regarding objectives, the main purpose of the PSUR is retrospective, integrated, post-authorisation benefit-risk assessment whilst that of the RMP is prospective pre-and post-authorisation benefit-risk management and planning. As such, the two documents are complementary.

When a PSUR and an RMP are submitted together, the RMP should reflect the conclusions of the accompanying PSUR. For example if a new signal is discussed in the PSUR and the PSUR concludes that this is an important identified or important potential risk to be added in the RMP, the important risk can be added in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimisation plan should be updated to reflect the marketing authorisation holder's proposals to further investigate the safety concern and minimise the risk.

V.B.10.1. Common modules between periodic safety update report and risk management plan

The proposed PSUR and RMP modular format is intended to minimise duplication by enabling common (sections of) modules to be utilised interchangeably across both reports. Common (sections of) modules are identified in Table V.4..

Table V.4. Common sections between RMP and PSUR (may not be in identical format)

RMP section	PSUR section
Part II, module SV – "Post-authorisation experience"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"

V.B.11. Principles for the assessment of risk management plans by competent authorities

The principal points that need to be considered when reviewing an RMP for a medicinal product are:

V.B.11.1. Safety specification

- Have all appropriate parts of the safety specification been included?
- Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues which have not been discussed in the safety specification?
- If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
- What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicinal product?
- Are there specific risks in addition to those not addressed in the RMP, i.e. misuse and abuse?
- Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?
- If a generic or hybrid application, have all safety concerns from the reference medicinal product been included in the safety specification or, if not, then has appropriate justification been provided?

V.B.11.2. Pharmacovigilance plan

- Are all safety concerns from the safety specification covered in the pharmacovigilance plan?
- Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
- Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?

- Are the safety studies that have been imposed by a competent authority as conditions clearly identified?
- If medication error can lead to a safety concern, does the RMP include appropriate proposals to monitor these?
- Are the proposed additional studies necessary and able to provide the required further characterisation of the risk(s)?
- When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are they feasible and non-promotional?
- Are appropriate timelines and milestones defined for the proposed actions, the submission of their results?

V.B.11.3. Plans for post-authorisation studies on efficacy

- Have all imposed PAES (as conditions of the MA or as specific obligations) been included?

V.B.11.4. Risk minimisation measures

- Is there a need for additional risk minimisation activities for any of the identified or potential risks?
- Have additional risk minimisation activities been suggested and if so, are they risk proportionate, is implementation feasible in all Member States and are the proposed activities adequately justified?
- Are the methods for evaluating the effectiveness of risk minimisation activities well described and appropriate?
- Have criteria for evaluating the success of additional risk minimisation activities been defined *a priori?*
- Has the marketing authorisation holder considered ways to reduce the likelihood of medication errors, when they can result in an important risk or lack of effectiveness? Has this been translated into appropriate risk minimisation measures?

V.B.11.5. Summary of the risk management plan

- Is it a true representation of the RMP?
- Have the facts been presented appropriately without promotional aspects?
- Are the content, format and language suitable for the intended audience?

V.B.11.6. When an RMP update is being assessed

- Have new data been discussed in the safety specification (e.g. removal of a safety concern following the submission of the final study results)?
- Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?
- Is there an evaluation of the effectiveness of risk minimisation measures?

- Have appropriate changes to risk minimisation measures been proposed if necessary?
- Is the summary of the RMP still appropriate?

V.B.12. Quality systems and record management

Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies with the marketing authorisation applicant/holder. As such the qualified person responsible for pharmacovigilance in the EU (QPPV) should be aware of, and have sufficient authority over the content. The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in GVP Module I. The marketing authorisation holder should maintain records of when RMPs were submitted to competent authorities and the significant changes between RMP versions. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by pharmacovigilance inspectors.

V.C. Operation of the EU network

V.C.1. Requirements for the applicant/marketing authorisation holder in the EU

For all new marketing applications, the applicant shall submit the risk management plan describing the risk management system, together with a summary thereof [DIR Art 8(3)(iaa)].

In the post-authorisation phase, an RMP update or a new RMP may need to be submitted at any time:

- at the request of the Agency or a competent authority in a Member State when there is a concern about a risk affecting the benefit-risk balance.
- with an application involving a change to an existing marketing authorisation when the data included leads to a change in the list of the safety concerns, or when a new additional pharmacovigilance activity or a new risk minimisation activity is needed or is proposed to be removed. The RMP update may be warranted as a result of data submitted with applications involving e.g. a new or significant change to the indication, a new dosage form, a new route of administration, a new manufacturing process of a biotechnologically-derived product.

The need for an RMP or an update to the RMP should be discussed with the Agency or a competent authority in a Member State, as appropriate, well in advance of the submission of an application involving a significant change to an existing marketing authorisation.

V.C.1.1. Risk management plans with initial marketing authorisation applications

For full initial marketing authorisation applications, all parts of an RMP should be submitted (see V.B.3.). For other types of initial marketing authorisation applications, the requirements for the RMP content follow the concept of proportionality to the identified risks and potential risks of the medicinal product, and the need for post-authorisation safety data; therefore certain parts or modules may have reduced content requirements or may be left empty where not applicable.

V.C.1.1.1. New applications under Article 10(1), i.e. "generic"

The elements for new applications under DIR Art 10(1) are as follows:

- RMP part I: The elements are the same as for initial MAA for a full application;
- RMP part II: there are 3 situations possible:

1. The originator product has an RMP: RMP modules S1-SVII may not be applicable. Module SVIII should include the summary of the safety concerns, in line with the originator product. If the applicant considers that the available evidence justifies the removal or the change of a safety concern, then data in module SVII should also be included to address the safety concern and detailing the applicant's arguments. Similarly, if the applicant has identified a new safety concern specific to the generic product (e.g. risks associated with a new formulation, route of administration or due to a new excipient, or a new safety concern raised from any clinical data generated), this should be discussed and the new safety concern detailed in module SVII.
2. Originator does not have an RMP but the safety profile of the originator product is published on the CMDh website[11]. The elements under point 1 above should be followed.
3. Originator does not have an RMP and the safety profile of the originator product is not published on the CMDh website: Full modules SVII and SVIII should be included in the RMP. Module SVII should critically analyse available relevant information (e.g. own pre-clinical and clinical data, scientific literature, originator's product information) and propose a list of important identified and potential risks as well as missing information.

- RMP part III: This should include a description of the routine pharmacovigilance activities, as detailed in V.B.5.1..

  The applicant is strongly encouraged to contribute to and participate in the planned or ongoing studies performed by the MAH of the originator product, when it is important that all available (prospective) data is collected in one study. This may be the case for instance when data from patients using the new product is important to further characterise the safety profile of the substance and enrolling patients in separate studies with the same or similar objectives creates an unnecessary burden on patients, clinicians or investigators (e.g. pregnancy registries, disease registries, any PASS evaluating long-term use).

  The competent authority may also consider imposing studies to be conducted for generics as applicable (e.g. within the context of referrals when generics are involved or as consequence of the outcome of a referral imposing a study to the originator).

- RMP part IV: This part of the RMP may be left empty unless a PAES has been imposed to be conducted for the generic product (e.g. following a referral).
- RMP part V: When the originator product does not have additional risk minimisation activities, a statement that the safety information in the product information of the generic is aligned with the originator product is sufficient for RMP part V. Where new risks have been identified for the generic product, the risk minimisation activities for such safety concerns should be presented in part V, following the same elements as for a full MA application.

  If the originator product does have additional risk minimisation activities, a full Part V is required for the generic product.

- RMP part VI: The elements are the same as for a full initial MAA.

[11] See http://www.hma.eu/464.html

- RMP part VII: The elements are the same for a full initial MAA. For RMP annexes 4 and 5, the applicant is strongly encouraged to use materials as similar, in content, as possible to the originator product.

V.C.1.1.2. New applications under Article 10c, i.e. "informed consent"

For new applications under DIR Art 10c, the RMP should be the same as the RMP of the cross-referred medicinal product. An RMP will still be required even if the cross-referred product does not have an RMP. If the MAH is the same as for the authorised product, the MAH is encouraged to put in place only one RMP document for their products with the same active substance.

V.C.1.1.3. New applications under Article 10(3), i.e. "hybrid"

For new applications under DIR Art 10(3), the RMP elements are the same as for a generic product. In case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, the applicant should discuss in RMP module SVII whether this results in the addition or deletion of a safety concern. Clinical trial data generated to support the application should be discussed in the RMP, as appropriate (e.g. RMP part II, modules SI, SIII). Other parts of the RMP should also be aligned (e.g. parts V and VI).

V.C.1.1.4. New applications involving fixed combination medicinal products

For new applications for fixed dose combinations, there are two situations:

1. The combination contains a new active substance: A full RMP, following the elements as for full initial MAA, should be submitted. RMP modules SI-SVI should focus on the new active substance.
2. The combination does not contain a new active substance: The RMP should follow the elements for a generic product. For the purpose of establishing the elements of RMP part II, "the originator" should be read as "any/all authorised products containing the same active substances included in the new product".

In addition, data on the fixed combination should be provided in modules SII and SIII.

V.C.1.1.5. New applications under Article 10a, i.e. "well established medicinal use"

For new applications under DIR Art 10a, RMP elements are as follows:

- RMP part I: The elements are the same as for a full initial MAA.
- RMP part II: Only RMP modules SVII and SVIII are required. The applicant is required to justify the proposed safety concerns, or the lack of any thereof, using available evidence from published scientific literature (information available in the public domain).
- RMP parts III-VII: The elements are the same as for a full initial MAA.

V.C.1.2. Risk management plans first submitted not as part of an initial marketing authorisation application

V.C.1.2.1. New risk management plans at the request of a competent authority to address one or more safety concerns

The elements are the same as those applicable to a generic product where the originator product does not have an RMP (see V.C.1.1.1.).

Two possible scenarios are envisaged:

1. MAHs may be requested to submit an RMP with a RMP module SVII focused on the safety concern(s) evaluated in the procedure. Other safety concerns should be included as needed.

2. MAHs may be requested to submit an RMP based on a comprehensive identification of safety concerns.

It is left to the discretion of the competent authority, which is the most appropriate in given circumstances.

V.C.1.2.2. Unsolicited risk management plan submission in post-authorisation phase

This RMP follows the elements of the type of MA under which this product was initially submitted (i.e. full marketing authorisation application, generic medicinal products, “informed consent” applications, etc., see V.C.1.1.).

V.C.2. Submission of a risk management plan to competent authorities in the EU

For centrally authorised products, the RMP should be submitted as PDF files within the eCTD submission. Following a Commission Decision where the procedure has involved the submission of an RMP, marketing authorisation holders should submit the RMP annex 1 in XML format within a specified timescale. RMP annex 1 provides the key information regarding the RMP in a structured electronic format which, following validation at the Agency, is uploaded into an Agency database that is accessible and searchable by the Agency and competent authorities in Member States. The system for nationally authorised products varies by Member State and their requirements should be followed.

Details of new submission requirements and the electronic format will be provided on the Agency and Member State websites as appropriate and may in future replace the requirements in the paragraph above.

The initial RMP should be submitted as part of the initial marketing authorisation, or if required, for those products that do not have an RMP, through the appropriate post-authorisation procedure.

V.C.2.1. Risk management plans updates

As stated in V.C.1.2. an RMP update is expected to be submitted at any time when there is a change in the list of the safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimisation activities. The significant changes of the existing additional pharmacovigilance and risk minimisation activities may include removing such activities from the RMP. For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP with the procedure triggering those changes.

An update of the RMP might be considered when data submitted in the procedure results in changes of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities, or of routine risk minimisation activities beyond routine communication. For example, an RMP might also be warranted with a significant change of the plans for annual enhanced safety surveillance (routine pharmacovigilance activity), or when monitoring of renal function is added as a recommendation in the *Special warnings and precautions for use* section 4.4 of the SmPC (routine risk

minimisation activity). The need to update the plans to evaluate the effectiveness of risk minimisation activities should also be considered with such updates.

When an emerging safety issue is still under assessment, in particular in the context of a signal, an RMP update may be required upon confirmation that this impacts the safety specification and should be updated as appropriate.

Unless requested otherwise, a track-changes RMP document should be included with every RMP update, showing changes introduced in the latest update (as applicable), as well as compared with the "current" approved version of the RMP.

A medicinal product can only have one "current" approved version of an RMP. If several updates to the RMP are submitted during the course of a procedure, the version considered as the "current" approved RMP for future updates and track-changes purposes shall be the one submitted with the closing sequence of the procedure.

When an RMP update is submitted with a procedure, the RMP is considered approved at the end of the procedure, when all changes are considered acceptable.

In the post-authorisation phase, submission of a new or updated RMP outside of another regulatory procedure constitutes a variation in accordance with the Guidelines on Variations[12]. For detailed guidance on relevant variation categories and their classification, please also refer to the Agency's Practical Questions and Answers to Support the Implementation of the Variations Guidelines in the Centralised Procedure[13].

RMP management with parallel procedures

If a medicinal product has more than one concurrently on-going procedure which requires submission of an RMP, ideally a combined RMP should be submitted with appropriate separation of data in RMP module SIII. The best regulatory path for the RMP update in case of multiple procedures potentially impacting on the RMP content should be discussed with the competent authority before submission.

RMP updates with the PSUR

If, when preparing a PSUR, there is a need for changes to the RMP as a result of new safety concerns, or other data presented in the PSUR, then an updated RMP should be submitted at the same time. In this case no stand-alone RMP variation is necessary. Should only the timing for submission of both documents coincide, but the changes are not related to each other, then the RMP submission should be handled as a stand-alone variation.

However, in the context of a PSUR EU single assessment (PSUSA), submission of RMP updates cannot be accepted together with the PSURs of medicinal products (centrally and/or nationally authorised). Marketing authorisation holders should take the opportunity of another upcoming procedure to update their RMP. Alternatively marketing authorisation holders should submit a separate variation to update their RMP.

For nationally authorised medicinal products, RMP updates should be submitted to the competent authorities in Member States for assessment.

[12] Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

[13] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000104.jsp&mid=WC0b01ac0580025b88.

V.C.3. Assessment of the risk management plan within the EU regulatory network

Within the EU, the regulatory oversight of RMPs for products authorised centrally lies with the Pharmacovigilance Risk Assessment Committee (PRAC). For products authorised nationally, the national competent authorities are responsible of the assessment of the RMP. For the RMP assessment, the PRAC appoints a PRAC rapporteur who works closely with the (Co-)Rapporteur(s) appointed by the CHMP or with the Reference Member State as appropriate. The EMA may, on a case-by-case basis, consult healthcare professionals and patients during the assessment of RMPs to gather their input on proposed risk minimisation measures.

The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in DIR Art 104(3)(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the national competent authority shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned [DIR Art 104a(2)].

For centrally authorised products, only additional risk minimisation measures recommended by the PRAC and subsequently agreed by the CHMP should be included in the risk minimisation plan. Additional risk minimisation measures are conditions of the marketing authorisation and in this respect, key elements are detailed in Annex II to the Commission Decision. In addition, exceptionally, certain conditions or restrictions with regard to the safe and effective use of the medicinal product may be imposed to the Member States through a Commission Decision in accordance with Article 127a for their implementation at national level.

When necessary, the competent authorities should ensure that marketing authorisation holders of generic and/or similar biological medicinal products make similar changes to their risk minimisation measures when changes are made to those of the reference medicinal product.

V.C.4. Implementation of additional risk minimisation activities

For products with additional risk minimisation activities, it is the responsibility of the marketing authorisation holder and national competent authority to ensure that all conditions or restrictions with regard to the safe use of the product in a particular territory are complied with.

Marketing authorisation holders are responsible for ensuring compliance with the conditions of the marketing authorisation for their product wherever it is used within the European Economic Area (EEA).

National competent authorities should also ensure that any conditions or restrictions with regard to the safe and effective use of a centrally authorised product are applied within their territory regardless of the source of the product.

However, individual Member States may have very different healthcare systems and medical practice may differ between Member States and consequently some risk minimisation measures may need to be implemented in different ways depending upon national customs and requires additional agreement with the Member States for their implementation (e.g. pregnancy prevention programme, controlled distribution, etc.). Therefore, for centrally authorised products, the legislation foresees that in addition to the Commission decision to marketing authorisation holder, there can be a Commission Decision to the Member States giving the Member States the responsibility for ensuring that specific conditions and/or restrictions for which key elements are provided in the Commission decision are implemented

by the marketing authorisation holder in their territory. For these specific risk minimisation activities, marketing authorisation holders are strongly encouraged to discuss the feasibility of how they might be implemented with individual national competent authorities during the building of the risk minimisation plan.

V.C.5. Transparency

The Agency and Member States shall make publically available, by means of the European medicines web-portal and the national medicines web-portals, public assessment reports and summaries of risk management plans [REG Art 26(1), DIR Art 106].

For centrally authorised products the Agency:

- makes public a summary of the RMP;
- includes tables relating to the RMP in the European Public Assessment Report (EPAR) including the product information and any conditions of the marketing authorisation.

The national competent authorities will provide details of how they intend to implement DIR Art 106.