28 March 2017
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Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems (Rev 2)

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This track-change version identifies the majority of changes introduced to the public consultation version of this document as the Agency's response to the comments received from the public consultation. This track-change version is published for transparency purposes and must not be taken or quoted as the final version.

* For this reason, the timetable above, and in particular the date of coming into effect, apply only the clean version published as final.

For the final version of this module and any future updates, please see the GVP webpage of the Agency's website.

Note: RMPs submitted for initial marketing authorisation applications and D121 responses applying GVP M V Rev 1 will be accepted for a further 6 months, and all other RMP submissions (including D91

responses for an initial application under accelerated assessment) will be accepted for one further year until 31 March 2018.

* Note: Revision 2 is a major revision with modifications throughout and contains the following:

- further clarification of what RMPs should focus on in relation to an important identified or important potential risk and missing information;
- removal of duplication within GVP Module V;
- removal of duplication of information in other guidance documents;
- further guidance on the expected changes in the RMP during the life cycle of the product;
- updated requirements for different types of initial marketing authorisation applications, with the aim to create risk-proportionate RMPs.

The guidance is updated in parallel to an amended RMP template for initial marketing authorisation application.

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V.A. Introduction

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-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 and risks 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~~document the ~~safety profile at different points in~~risk management system considered necessary to identify, characterise and minimise 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.~~important risks. To this end, the RMP contains ~~the following~~:

1. the identification or characterisation of the safety profile of the medicinal product ~~including what is known~~, with emphasis on important identified and ~~not known~~ important potential risks and~~,~~ ~~importantly,~~ missing information, and also on which ~~risks~~ safety concerns need to be ~~further characterised or~~ managed proactively or further studied (the 'safety specification');
2. the 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. the planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

As knowledge regarding a medicinal product's safety profile increases over time, so will the risk management plan change.

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~~),~~)(cb) and (cc), REG Art 10a(1)(a) and (b), DIR Art 21a~~,~~(b) and (f), DIR Art 22a(1)(a) and (b)] and for these studies to be included in the risk management system [REG 14a, DIR Art 22c~~,~~(1), IR Art 30(1)(d)]. The legislation also includes provisions for additional risk minimisation activities to be included in the risk management system as a condition to the marketing authorisation [REG Art 9(4)(ca), DIR Art 21a~~].~~(a)]. 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 and GVP Module XVI Addendum I on educational materials.

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".

[1] See www.ema.europa.eu

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~~DIR: Article 8(3)(ia) and (iaa), Article 21a, Article 22a~~,~~ (1), Article 22c~~,~~ (1), Article 104~~,~~ (3), Article 106(c), Article 127a;
- ~~Regulation (EC) No 726/2004~~REG: Article 6(1), Article 9(4)(c), (ca), (cb), (cc), Article 10a~~,~~ (1), Article 14a, Article 26(1)(c);
- ~~Commission Implementing Regulation (EU) No 520/512~~IR: Article 30, Article 31, Article 32, ~~Articles~~Article 33, Annex ~~1~~I;
- Regulation (EC) No 1901/2006 Article 34~~;~~ (2);
- Regulation (EC) No 1394/2007 Article 14~~.~~ (2).

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~~ The definitions from Guideline on good pharmacovigilance practices: Annex I - Definitions apply also for the purpose of this GVP Module. However, the RMP should focus on those risks that are relevant for the risk management activities for the authorised medicinal product.

From the **identified risks** of the medicinal product, the RMP should address only the risks that are undesirable ~~outcome~~clinical outcomes and for which there is sufficient scientific evidence that ~~it is~~they are caused by the medicinal product.

~~In a clinical trial, the comparator~~Reports of adverse reactions may be ~~placebo, active substance or~~ derived from multiple sources such as 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~~clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature. They may be linked to situations such as off label use, medication errors or drug interactions. Not all reported adverse reactions are necessarily considered a relevant risk of the product in a given therapeutic context.

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

~~An~~**risks** of the medicinal product, the RMP should address only the risks that are undesirable ~~outcome~~clinical outcomes and for which there is ~~a~~ scientific ~~basis for supposition~~evidence to suspect the possibility of a causal ~~relation~~relationship 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 currently insufficient ~~support~~evidence to conclude that ~~there is a causal~~ this association~~.~~ is causal.

~~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~~ The RMP should focus on the **important identified risks** that are likely to have an impact on the risk-benefit ~~risk~~ balance of the product ~~when~~

~~further characterised and/or if not managed appropriately in daily clinical practice, and which therefore~~. An important identified risk to be included in the RMP would usually ~~lead to further~~warrant:

- 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'.~~

- Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk (see V.B.8.), or additional risk minimisation activities.

The **important potential risks** to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Where there is a ~~justified supposition~~scientific rationale that an adverse ~~reaction~~clinical outcome 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)~~, or resulting from the long-term use of the product, the adverse reaction should be considered a potential risk, and if deemed important, should be included in the ~~RMP~~ list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

Missing information ~~in the RMP (within this Module referred~~relevant to ~~as "missing information")~~

~~Gaps~~the risk management planning refers to gaps in knowledge about the safety of a medicinal product~~, related to the~~ for certain anticipated utilisation ~~patterns such as~~ (e.g. long-term use) or for use in particular patient populations, for which ~~could be clinically significant. For instance:~~

- ~~safety profile with long-term use when~~ there ~~are suspected potential risks related~~is insufficient knowledge to ~~cumulative or long-term exposure;~~
- ~~use is anticipated in populations not studied (e.g. pregnant women or patients with severe renal impairment) and~~determine whether the safety profile ~~is expected to be different in these populations;~~
- ~~off-label use is likely; if a markedly different safety profile than~~differs from that ~~in the target~~ characterised so far. The absence of data itself (e.g. exclusion of a population ~~is suspected, the specific~~ from clinical studies) does not automatically constitute a 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~~. Instead, the 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~~ planning should focus ~~described above for the EU GVP.~~ on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

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.):~~V.A.1. and V.B.5.8.):

- 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~~reclassified to 'important identified risks' (e.g. if ~~they result in associated additional risk minimisation activities~~scientific and clinical data strengthen the association between the risk and the product).
- In certain circumstances, where the risk is fully characterised and appropriately managed, important identified risks may ~~need to~~ be removed from the safety specification (e.g. for products marketed for a long time for which ~~risks~~there are no outstanding additional pharmacovigilance activities and/or the ~~required~~ risk minimisation activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice ~~thus reducing the~~

~~risk to a level when is no longer considered an important risk~~, such as inclusion into treatment protocols or clinical guidelines).

- Given the overall aim of obtaining more information regarding the risk-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~~might 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~~With the exception of some patient registries ~~and programmes (such as pregnancy prevention programmes),~~, it is expected that 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.~~

The need to continue additional risk minimisation activities may change, as the recommendations for specific clinical measures to address the risk become part of the routine practice such as inclusion into standard treatment protocols in the EU, or in response to the findings of effectiveness of risk minimisation evaluations (i.e. they may need to be replaced with more effective activities). Some risk minimisation activities might be needed to be retained for the lifetime of the medicinal product (e.g. pregnancy prevention programmes).

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); DIR Art 104(3)(c)];
- ensuring that the knowledge and understanding ~~gained regarding~~on the product's safety profile, following its use in clinical practice ~~is~~, are 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 risk-benefit ~~risk~~ balance of medicinal products [Dir Art 104(3)(e)], and update the risk management system and the RMP accordingly, as described below. The critical review of the 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~~milestones when the marketing authorisation holders of products approved following full initial marketing authorisation applications 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).~~

  – with the (first) 5-year renewal;

- in the time period when the first PSUR following the first 5 year renewal is due for submission. It is anticipated that this PSUR submission would occur approximately 8-9 years following the granting of the marketing authorisation, at the time when the assessment of the initial marketing authorisation applications for generic products for the active substance commences. As such, the safety profile of the medicinal product is likely to be sufficiently well characterised to allow for a critical review and update of the list of safety concerns.

V.B.3. ~~Format~~Overview of the format and ~~contents~~content of the risk management plan (RMP)

The RMP consists of seven parts. The submitted RMP shall follow the RMP template [IR Annex I]. 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~~the update of the RMP~~. In~~; in addition, in specific circumstances certain RMP modules may have reduced content requirements (see ~~V.C.2.1.)~~.V.C.1.1.). However, the RMP document is expected to be submitted as one single document including all modules and annexes, as relevant.

~~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.~~Table V.1. [IR Annex I]:

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

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

The amount of information, particularly in RMP part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its life cycle (by reference to DIR Art 8(3)).

Article 14(2) of Regulation (EC) No 1394/2007 provides for a specific framework for RMP for advanced therapy medicinal products (ATMP). The marketing authorisation applicants/holders should adapt the risk management plans of ATMP, considering and discussing the anticipated post-authorisation follow-up needs, focusing on particularities of these medicinal products. The specific RMP content requirements for ATMP should be discussed with the competent authority before the submission. Further guidance on the safety and efficacy follow-up and risk management requirements for ATMP is provided on the Agency's website[3].

It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/marketing authorisation holder containing the same active substance(s) (i.e. the RMP is an active substance-based document) [IR Art 30(2)].

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~~ in the dossier, unless the sections are intended to be common modules with other documents such as the PSUR. 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 or references to relevant sections of the non-clinical and clinical overviews and summaries should be included in the RMP~~ core document~~.

[3] See www.ema.europa.eu; further ATMP-specific guidance is being developed

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 discussion.

To aid consistency between the information provided in the ~~eCTD~~dossier and the RMP, ~~Table V.2.~~Table V.2. indicates where information from the eCTD is likely to be discussed in the RMP~~:~~. The eCTD data refers to the submission containing the RMP (e.g. initial marketing authorisation applications and major variations) or to historical data already included in the dossier with previous submissions.

In the context of a centralised procedure, the RMP should be submitted as part of an eCTD submission; however, for non-centralised procedures the RMP submission might still be part of a CTD submission. eCTD data/submissions in this Module should be read as eCTD or CTD data/submission, corresponding to the type of submission to the competent authority.

Table V.2. Mapping between RMP modules and information in 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 SVI "Additional EU requirements for the safety specification"	Data not presented elsewhere in eCTD
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~~Only key literature referenced in the RMP should be included in RMP annex 7. This should be in the format of electronic links or references if already included elsewhere in eCTD (see ~~V.B.9.)~~.V.B.10.).

The description of the parts and modules of an RMP in V.B.4. provides guidance on the main topics to be ~~covered~~addressed 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~~scientifically based and should not include any element of a promotional nature.

~~V.B.3.1.~~The preliminary section of the RMP should include the following administrative information about the RMP document:

~~*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;
- sign off 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~~The evidence of oversight from the qualified person for pharmacovigilance (QPPV) is not needed for versions submitted for assessment. The QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalised approved version of the document; for eCTD submissions this would be the RMP with the last eCTD sequence of the procedure (e.g. closing sequence). The evidence of QPPV oversight can take the form of a statement that the RMP has been reviewed and approved by the marketing authorisation holder/applicant's QPPV and that the electronic signature is on file.

V.B.4. 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. The information should include:

Active substance information:

- active substance(s);
- pharmacotherapeutic group(s) (ATC code);
- name of the:
  - marketing authorisation applicant - for initial marketing authorisation applications;

or

– marketing authorisation holder - for RMPs submitted with post-authorisation procedures;

- for mutual recognition/ decentralised procedures applications: the name(s) of the expected future marketing authorisation holder(s) in the reference Member State, if known at the time of the application;
- medicinal product(s) to which this RMP refers.
- authorisation procedure(s) (centralised, 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~~proposed product information, as appropriate;
- ~~indications;~~
- indications: approved and proposed (if RMP submitted with an extension/restriction of indication);
- 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~~5. 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~~include 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 any outstanding safety questions that warrant further investigation to refine the understanding of the risk-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~~in V.B.5.2.-V.B.5.9. 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.C.1.1..

V.B.~~4~~5.1. General considerations for generic products and advanced therapy medicinal products

V.B.~~4~~5.1.1. 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[4]. The CMDh has published the summary of safety concerns for selected medicinal products for which an RMP is in place, on the CMDh website[5].~~ 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~~5.1.2. 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~~concern with other medicinal products including risks to living donors, risks of germ line transformation and

~~[4] See http://www.cma.europa.eu.~~
~~[5] See http://www.hma.eu/464.html.~~

transmission of vectors. ~~This needs~~These risks need to be taken into consideration when developing the safety specification for ATMPs~~.~~ (see V.B.5.8.).

V.B.45.2. RMP part II, module SI "Epidemiology of the indication(s) and target population(s)"

This RMP module should include incidence, prevalence, outcome of the (untreated) 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~~epidemiology varies across regions~~.~~).

This section should also describe the relevant adverse events to be anticipated in the (untreated) target population in EU, 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 should not ~~be~~include any element of a promotional nature.

~~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.45.3. RMP part II, module SII "Non-clinical part of the safety specification"

This RMP module should present a high-level summary of the ~~important~~significant 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 non-clinical 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 potential 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~~.~~, but the safety finding is not expected to be carried forward to SVII and SVIII as a safety concern.

If, based on the assessment of the non-clinical or clinical data, additional non-clinical studies are considered warranted and proposed to be part of the pharmacovigilance plan, 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.

The content of this section should be assessed for relevance over time. Post-authorisation, this section would only be expected to be updated when new non-clinical data impact the list of safety concerns. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed when sufficient relevant post-marketing experience and evidence are gathered, can be removed from the list of safety concerns.

V.B.5.4.~~4.~~ RMP part II, 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).~~ tables/graphs) at time of submission of the initial RMP or when there is a major update due to new exposure data from clinical studies (e.g. in a new indication). The content of this section should be assessed for relevance over time and, in the absence of new significant clinical trial exposure data, this section does not need to be updated.

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~~.~~ (e.g. ethnic origin).

Paediatric data should be divided by age categories (e.g. ICH-E11[6]); 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

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

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 of administration, 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.~~5.5. RMP part II, 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~~Information on the ~~relevant subpopulations, including whether or not any use in~~ low exposure of special populations ~~excluded from~~or the ~~clinical trials~~lack thereof (e.g. pregnant women ~~of childbearing potential, older people) might be associated with~~, breast-feeding women, patients with renal impairment, hepatic impairment or cardiac impairment, populations with relevant genetic polymorphisms, immuno-compromised patients and populations of 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, as available.

If the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different ~~list of~~ safety ~~concerns and~~profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP.

Excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e. "on-label", and if the use in such populations might be associated with risks of clinical significance. 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. When such populations are proposed as missing information, then RMP module SIV should also include a discussion on the relevant subpopulations.

~~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.~~

If there is evidence that use in excluded populations is associated with an undesirable clinical outcome, then the outcome should be included as an important (potential) risk.

V.B.~~4~~5.6. RMP part II, 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 or from other authorised products containing the same active substance, from the same marketing authorisation holder, 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~~-label 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 from indications not authorised in EU should also be summarised, and the implications for the authorisation in the EU should be discussed.

V.B.~~4~~5.7. RMP part II, module SVI "Additional EU requirements for the safety specification"

~~Some~~ In addition to safety topics ~~were not included in the~~ required by ICH-E2E ~~format, but are thought to~~ (see GVP Annex IV), the following should be ~~of particular interest due to either EU legislation or prior experience of a safety issue. This includes:~~

addressed in the EU-RMP: the potential for misuse for illegal purposes, and, where appropriate, the proposed ~~means of limiting this;~~risk minimisation measures, e.g. limited pack size, controlled ~~distribution~~access programme, special medical prescription [DIR Art 71(2)] (see also ~~V.B.7.)~~.V.B.8.).

V.B.~~4~~5.8. RMP part II, 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~~The following safety topics derived from specific situations/data sources are thought to be of particular interest ~~to be discussed~~ for the risk identification discussion in module SVII, ~~as appropriate~~and should be discussed when they lead to risks of the product:

- *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, the important risks following overdose should be included as ~~a~~ safety ~~concern~~concerns 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 leading to important risks, 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~~Practice Guide on ~~recording, coding, reporting~~Risk Minimisation and ~~assessment~~Prevention of ~~medication errors~~[7] ~~including in "~~Medication Errors , Annex 2 - Design features which should be considered to reduce the risk of medication error~~"~~[8] which includes an extensive list of potential

~~[7] EMA/762563/2014; available on EMA website http://www.ema.europa.eu~~
[8] EMA/606103/2014; http://www.ema.europa.eu

medication errors and the consequence to the patients. ~~Adverse reactions~~Important risks 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~~ due to 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 with the view of considering them as important potential risks;

- *potential for off-label use* ~~should be discussed with a focus on any anticipated~~, when differences in safety concerns between the target and the off-label population~~. Off-label use is particularly relevant in situations where~~ are anticipated, 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~~if an important identified or potential *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;

- *important 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~~.~~, and plans to further characterise and minimise the risks described. Important ~~(potential) risks following clinically important~~risks derived from interactions should be ~~considered for inclusion~~included 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~~,~~. and GVP Module XVI;

- *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~~.~~;

- risks associated with the disposal of the used product (e.g. transdermal patches with remaining active substance or remains of radioactive diagnostics);

- risks related to the administration procedure (e.g. risks related to the use of a medical device (malfunction which impacts on the dose administered, risk of variability in complex administrations);

- paediatric safety issues that are particular causes of concern in paediatric population, as described in section 5 of Annex I of the PIP opinion (Potential long-term safety/efficacy issues in relation to paediatric use for consideration in the RMP/Pharmacovigilance activities).

For RMPs of ~~advanced therapy medicinal products (~~ATMPs~~),~~ the applicants should also consider the ~~following~~ possible specific risks in drafting the safety specifications (see Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products[9]~~):~~).

~~• 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);~~

[9] 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~~5.8.1. RMP part II, 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 submission of an RMP, either at the time of the initial marketing authorisation (MA) application~~,~~ or ~~with a new RMP submitted~~ post-authorisation (~~at the competent authority's request or without request~~i.e. for approved products that previously did not have an RMP).

This section is expected to be "locked" and not change after the approval of the initial RMP.

V.B.45.8.1.a. RMP part II, module SVII sections "Risk considered important for inclusion in the list of safety ~~specification~~concerns" and "Risk not considered important for inclusion in the list of safety ~~specification~~concerns"

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);~~
- risk seriousness;
- risk frequency;
- ~~clinical and~~ the risk-benefit ~~risk~~ impact~~;~~ of the risks.

~~[for~~For risks not taken forward as safety concerns~~] the justification~~, the information can be grouped by reasons for not including them as ~~a~~ safety ~~concern~~concerns.

V.B.45.8.2. RMP part II, module SVII section "~~Identification of~~New safety concerns and reclassification 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)***~~

In the post-authorisation phase, it is expected that new identified and potential risks of the product are presented in the safety section of the dossier (with e.g. signal evaluation, periodic benefit-risk evaluation, or safety variations procedures) together with an evaluation on whether the risks should be considered important and added in the Safety Specification in the RMP. This discussion should not be duplicated in the RMP, but the details of any new important identified or potential risk should be included in the RMP section described in V.B.5.8.3..

When an important identified or potential risk or missing information is re-classified or removed, a justification should be provided in this RMP section, with appropriate reference to the safety data. The information included in this section may take the form of a statement describing a previous regulatory request, with a reference to the procedure where such request was formulated.

V.B.45.8.3. RMP part II, module SVII section "Details of important identified ~~and~~risks, important potential risks, and missing information"

For RMPs ~~covering~~containing multiple products ~~where~~, if there ~~may be~~are significant differences ~~in the identified and potential risks or missing information for different~~between 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 risks 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~~ characterisation of the ~~individual patient (~~risk: e.g. frequency, absolute risk, relative risk, severity, reversibility, ~~and~~ long-term outcomes, ~~as well as~~impact on 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 risk-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).~~

- description of a population in need of further characterisation, or description of the risk anticipated in the population not studied, as appropriate.

V.B.45.9. RMP part II, 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.56. RMP part III "Pharmacovigilance plan" (including post-authorisation safety studies)"

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~~safety concerns in the safety specification. It provides a structured plan for:

- the investigation of whether a potential risk is ~~real or not~~confirmed as an identified risk or refuted;
- 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~~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.56.1. 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.~~DIR and REG. 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~~)~~), or national competent authorities 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~~standard 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, and NCAs 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"~~standard 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~~6.1.1.- 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~~to provide useful data for the analysis of the reports, which are relevant for regulatory decisions, while decreasing 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~~6.1.2. -Other forms of routine pharmacovigilance activities

~~Other~~The description of the planned other forms of routine pharmacovigilance activities ~~to~~should be described in this section ~~include~~. e.g. the high level description of the enhanced passive surveillance~~, requested~~ system, 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~~6.2. RMP part III section "Additional pharmacovigilance activities"

~~For each safety concern, the~~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 risk-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 should not ~~be~~include any element of a promotional nature.

~~Pharmacoepidemiology studies included~~Studies in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place, and 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,~~Study protocols may be included for evaluation in an RMP update only when the studies are included in the pharmacovigilance plan and the protocols submission has been requested by the competent authority. Reviewed and approved 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~~C (or electronic links or references to 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~~included in other section of the eCTD dossier). Other category 3 studies protocols, submitted for information only ~~(~~, may also be included in RMP annex 3 – part C. Protocols of completed studies should be removed from RMP annex 3 once the final study reports are submitted to the competent authority for assessment and the study is removed from the Pharmacovigilance Plan.(see ~~V.B.10.)~~. V.B.10.3.).

~~Milestones, including a time point~~The milestones for the final study report submission to the competent authority~~,~~ should be included~~.~~ for all studies in the Pharmacovigilance Plan.

Marketing authorisation holders may also submit to EMA or national competent authorities protocols of post-authorisation safety studies (PASS) for Scientific Advice.

V.B.~~5~~6.3. 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~~to the marketing authorisation, either because they are key to the risk-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~~marketing authorisation 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 DIR Art ~~107 (m) (~~107m-q~~) of Directive 2001/83/EC~~ and the format and content of such non-interventional PASS should be as described in IR Annex III (see GVP Module VIII).

Other studies might be required in the RMP to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities. Such studies included in the pharmacovigilance plan are also 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.~~

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"*	☑Yes, in Annex IID	1	Mandatory and subject to penalties	No	No
	Non-interventional	☑Yes, in Annex IID			☑Yes	☑Yes
Specific obligation	"Interventional"*	☑Yes, in Annex IIE	2	Mandatory and subject to penalties	No	No
	Non-interventional	☑Yes, in Annex IIE			☑Yes	☑Yes
Required	"Interventional"*	No	3	Legally enforceable	No	No
	Non-interventional	No			☑Yes	No

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

Studies required in jurisdictions outside the EU should not be included in the RMP unless they are also imposed as a condition to the marketing authorisation or as a specific obligation, or required by the Agency or a national competent authority. Studies not required by the EMA or a 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.

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

V.B.~~6~~7. RMP part IV "Plans for post-authorisation efficacy studies"

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

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

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

- ~~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~~8. RMP part V "Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)"

~~This part~~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. i.e.~~, 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~~; products where risks differ according to the target population; products with different legal status for the supply of medicinal products to patients.

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.)~~V.B.8.). Guidance on additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures is provided in GVP Module XVI~~.~~ and GVP Module XVI Addendum I – Educational materials.

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~~professionals 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~~undesirable effects of the medicinal product, so that an informed decision on the treatment can be made;
- ~~**routine risk minimisation activities beyond routine** **recommending specific clinical measures to address the** **risk~~ ~~**communication**~~**:** usually found in sections 4.2 and 4.4 of the SmPC but can also be found in sections 4.~~6~~1, 4.3, 4.5, 4.6, 4.7 and 4.~~5~~9, and ~~accordingly~~ sections 2 and 3 of the PL; warning and precaution messages and recommendations in the SmPC will include information on ~~minimising~~addressing 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~~specific 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~~recommending 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~~medical 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~~medicinal product 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~~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~~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~~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~~reviewed.

~~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~~key messages of additional risk minimisation activities should be provided in RMP Annex 6 – ~~Protocols for proposed and on-going studies in categories 1-3~~Details of ~~the section "Summary table of~~ proposed additional ~~pharmacovigilance~~risk minimisation 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~~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 EU 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 in the RMP 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~~8.1. 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), including individual objectives and justification of why needed~~; for each additional risk minimisation activity, the following information on measuring~~ , and how 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;~~measured.
  - ~~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~~8.2. 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 [10].

V.B.~~8~~9. 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~~1)].

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 medicinal products, the Agency should publish the RMP summary on the EMA website at the time of the European Commission ~~Decision~~decision together with the other documents of the European Public Assessment Report (EPAR) of that ~~medicine.~~medicinal product. For nationally authorised medicinal products, a summary of the ~~RMPshould~~RMP should 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 identified or potential 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 or routine risk minimisation activities recommending specific clinical measures to address the risk;
- major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

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[11]. 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~~medicinal product and what it is ~~used~~authorised for;

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

[11] 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])

- summary of safety concerns and missing information;
- routine and additional risk minimisation measures;
- additional pharmacovigilance activities.

V.B.~~9~~10. 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~~10.1. RMP annex 1

Annex 1 of the RMP is the structured electronic representation of the EU ~~Risk Management Plan.~~risk management plan. It is not required to be submitted in eCTD, the electronic file should be submitted in accordance to ~~V.C.2..~~V.C.2. and the applicable guidance ~~on EudraVigilance~~[~~12~~13]. This annex can be left empty in the RMP document.

V.B.~~9~~10.2. RMP annex 2: Tabulated summary of planned, on-going, and completed ~~pharmacoepidemiological~~pharmacovigilance 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:

- Planned and ongoing studies, including objectives, safety concern addressed, and the planned dates of submission of intermediate and final results~~;~~.
- ~~completed~~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.~~

V.B.~~9~~10.3. 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).~~i.e. not in the Pharmacovigilance Plan). This annex may include the electronic links or references to other modules of the eCTD dossier where the protocols are included, instead of the full protocol documents.

~~[12] See http://eudravigilance.ema.europa.eu/human/EURiskManagementPlans.asp~~
[13] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000683.jsp&mid=WC0b01ac058067a113

V.B.~~9~~10.3.1. RMP annex 3 – part A: ~~Protocols~~ Requested protocols of ~~proposed~~ studies in the Pharmacovigilance Plan, 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~~If protocols have been requested to be submitted for review by the competent authority, and the marketing authorisation holder choses to submit for assessment a study protocol within the same procedure ~~the RMP has been submitted in. This~~as the RMP submission, part A should include this protocol; alternatively the protocol might be reviewed in a stand-alone procedure, and once agreed, included in the RMP annex 3 – 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~~ for the protocol submission should be agreed with the competent authority.

V.B.~~9~~10.3.2. RMP annex 3 – part B: ~~Updates~~Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, 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~~If protocols amendments have been requested to be submitted ~~within the RMP~~ for review by the competent authority, and the marketing authorisation holder choses to submit for assessment the study protocol amendment within the same procedure as the RMP submission, part B should include the updated protocol; alternatively the protocol amendment might be reviewed in a stand-alone procedure ~~before its integration in the RMP~~, and once agreed~~.~~, included in the RMP annex 3 – part C. The regulatory pathway ~~is to~~for the protocol submission should be agreed with the competent authority.

Once approved, protocols from parts A or B should be moved to part C, with the next warranted RMP update.

V.B.~~9~~10.3.3. RMP annex 3 – part C~~——~~

: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

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

- ~~the~~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~~electronic link or reference to other modules of the eCTD dossier where the protocols have been previously submitted, instead of the full protocol documents.
- ~~the~~The final protocols of other category 3 studies~~,~~: protocols that were not requested to be reviewed by the competent authorities~~,~~ and are submitted by the ~~MAH~~marketing authorisation holder 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~~10.4. RMP annex 4: Specific adverse event follow-up forms

This annex should include all follow-up forms used by the ~~MAH~~marketing authorisation holder 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~~10.5. RMP annex 5: Protocols for proposed and on-going studies in RMP part IV

This annex should include links or reference to other parts of the eCTD dossier, where the protocols for an imposed efficacy study ~~protocols~~ are already included, ~~if such~~for studies ~~were required~~included in RMP part IV.

V.B.~~9~~10.6. RMP annex 6: Details of proposed additional risk minimisation activities

If applicable~~:~~

~~***V.B.9.6.1. RMP, this 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~~10.7. 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 or reference to other documents included in other modules of the dossier.

~~V.B.10.~~V.B.10.8. RMP annex 8: "Summary of changes to the risk management plan over time"

A list of all significant changes to the RMP in chronological order should be provided in this annex. This should include a brief description of the changes and the date and version number of the RMPs when:

- safety concerns were added, removed or reclassified;
- studies were added or removed from the pharmacovigilance plan;

- risk minimisation activities recommending specific clinical measures to address the risks or additional risk minimisation activities were modified in the risk minimisation plan.

V.B.11. 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).~~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 risk-benefit ~~risk~~ assessment whilst that of the RMP is prospective pre-and post-authorisation risk-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~~Table V.4. 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 (~~ modules containing similar information (however, may not be in identical format and may not be interchangeable)

RMP section	PSUR section
Part II, Module SIII –"Clinical trial exposure"	Sub-section 5.1 "Cumulative subject exposure in clinical trials"
Part II, ~~module~~Module SV ~~– "~~–"Post-authorisation experience"	~~Section 3 – "Actions taken in the reporting interval for safety reasons"~~Sub-section 5.2 "Cumulative and interval patient exposure from marketing experience"
Part II, Module SVII – "Identified and potential risks" and Part II, Module SVIII – "Summary of the safety concerns"	Sub-sections 16.1 "Summaries of safety concerns" and 16.4 "Characterisation of risks"
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~~At the request of the Agency or a ~~-~~competent authority in a Member State when there is a concern about a risk affecting the risk-benefit ~~-risk~~ balance.
- ~~with~~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~~such as 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.).~~V.B.4.). 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~~;~~ [DIR Art 8(3)]; therefore certain parts or modules may have reduced content requirements or may be left empty, where not applicable.

Table V.~~C.1.1.1.~~**6.** Summary of minimum RMP requirements for initial marketing authorisation applications (for full description see text below)

Product	Part I	Part II								Part III	Part IV	Part V	Part VI
		SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
0. Full MA application	√	√	√	√	√	√	√	√	√	√	√	√	√
1. Generic product	√							‡	√	√	*	∫	√
2. Informed consent product	√	√	√	√	√	√	√	√	√	√	√	√	√
3. Hybrid product	√	†		†				†	√	√	√	∫	√
4.a. Fixed combination product – new active substance	√	‾	‾	‾	‾	‾	‾	√	√	√	√	√	√
4.b. Fixed combination product – no new active substance	√		†	†				‡	√	√	*	∫	√
5. Well established medicinal use product	√							√	√	√	√	√	√
6. Biosimilar product	√		√	√	√	√	√	√	√	√	√	√	√

√ = applicable/relevant

‡ = relevant only if "originator" product does not have an RMP and its safety profile is not published on CMDh website

* = relevant only when a PAES was imposed for the "originator" product

∫ = statement of alignment of safety information in PI is sufficient

† = requirements based on risk proportionality principle, addressing new data generated or differences with the "originator" product

Ŧ = focus on the new active substance

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~~marketing authorisation application for a full application;
- RMP part II: there are 3 situations possible:

1. The originator product has an RMP: RMP modules ~~S1~~SI-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~~ The originator product does not have an RMP but the safety ~~profile~~concerns of the ~~originator product is~~substance are published on the CMDh website14. The elements under point 1 above should be followed. If more than one list of safety concerns published on CMDh website apply for the same active substance, the applicant should justify the choice of proposed safety concerns in Module SVIII.
3. ~~Originator~~ The originator product does not have an RMP and the safety ~~profile~~concerns of the ~~originator product is~~substance are 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~~originator product'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.~~V.B.6.1..

The applicant is strongly encouraged to contribute to and participate in the planned or ongoing studies performed by the ~~MAH~~marketing authorisation holder of the originator product, when it is important that all available (prospective) data ~~is~~are collected in one study. This may be the case for instance when data from patients using the new product ~~is~~are important to further

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

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~~generic products as applicable (e.g. within the context of referrals when ~~generics~~generic products are involved or as consequence of the outcome of a referral imposing a study to the originator product).

- 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 product 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~~marketing authorisation 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~~marketing authorisation application, to the extent of data requested and provided in other parts of the RMP, as per above.
- RMP part VII: The elements are the same for a full initial ~~MAA~~marketing authorisation application. 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~~marketing authorisation holder is the same as for the authorised product, the ~~MAH~~marketing authorisation holder 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~~However, for 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 under Article 10b, i.e. involving "fixed combination" medicinal products

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

~~1.~~4. The combination contains a new active substance: A full RMP, following the elements as for full initial ~~MAA~~marketing authorisation application, should be submitted. RMP modules SI-SVI should focus on the new active substance.

~~2.~~5. 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 product" should be read as "any/all authorised products containing the same active substances included in the new product".

In addition, new data ~~on~~generated with 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~~marketing authorisation application.
- RMP part II: Only RMP modules SVII and SVIII ~~are required~~might be applicable. 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~~marketing authorisation application.

V.C.1.1.6. New applications under Article 10(4), i.e. "biosimilar products"

For new applications for biosimilar products, the RMP elements are described in GVP Product or Population Specific Considerations II: Biological medicinal products.

V.C.1.1.7. New applications for homeopathic and herbal products not falling within the scope of the simplified registration

New applications for homeopathic and herbal medicinal products not falling within the scope of the simplified registration are subject to standard marketing authorisation; therefore the RMP elements are the same as defined by the type of the marketing authorisation application (i.e. legal basis).

V.C.1.2. Risk management plans first submitted ~~not as part of an initial marketing~~ post-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~~Marketing authorisation holders 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~~Marketing authorisation holders 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~~marketing authorisation under which this medicinal product was initially submitted (i.e. full marketing authorisation application, generic medicinal products, "informed consent" applications, etc., see ~~V.C.1.1.).~~V.C.1.1).

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

For centrally authorised medicinal products, the RMP should be submitted as PDF files within the eCTD submission. Following a Commission ~~Decision~~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 the competent authorities in the Member States. The system for nationally authorised medicinal products varies ~~by~~across Member ~~State~~States and ~~their~~the national requirements should be followed.

Details of new submission requirements and the electronic format will be provided on the Agency and Member ~~State~~State's 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~~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 or is expected to result in changes of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities, or of routine risk minimisation activities ~~beyond routine communication.~~recommending specific clinical measures to address the risk. For example, an RMP update 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~~,~~ (as defined in GVP Module VI - Management and reporting of adverse reactions to medicinal products), in particular in the context of a signal or potential risk that could be an important identified risk, an RMP update may be required ~~upon confirmation that this impacts~~if the emerging safety ~~specification and should be updated as appropriate~~issue is confirmed and the important identified or potential risk requires to be added to the list of safety concerns in the RMP.

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[15]. 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[16].

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 the Member States for assessment.

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

Within the EU, the regulatory oversight of RMPs for medicinal products authorised centrally lies with the Pharmacovigilance Risk Assessment Committee (PRAC). ~~For products authorised nationally, the~~

[15] 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.
[16] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000104.jsp&mid=WC0b01ac0580025b88.

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 and CAT (for ATMPs) 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.

For medicinal products authorised nationally, the national competent authorities are responsible of the assessment of the RMP. The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system for each medicinal product, 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 medicinal products, only additional risk minimisation measures recommended by the PRAC and subsequently agreed by the CHMP should be included in the risk minimisation plan. as additional risk minimisation activities. Additional risk minimisation measures are conditions ofto the marketing authorisation and in this respect,; key elements are detailed in Annex II to the Commission Decisiondecision. 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 Decisiondecision in accordance with ArticleDIR Art 127a for their implementation at national level.

When necessary, the competent authorities should ensure that all marketing authorisation holders of generic and/or similar biological medicinal products containing the same active substance 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.*~~*V.C.4.* *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)(c), DIR Art 106~~].~~(c)].

For centrally authorised medicinal 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~~to the marketing authorisation.

The national competent authorities will provide details of how they intend to implement the transparency measures at national level [by reference to DIR Art 106~~.~~].