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Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems

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V.A. Introduction

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk balance is judged to be positive for the target population. A typical medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post-authorisation. Planning of the necessary pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles.

However, the purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore risk management has three stages which are inter-related and re-iterative:

1. Characterisation of the safety profile of the medicinal product including what is known and not known.
2. Planning of pharmacovigilance activities to characterise risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product.
3. Planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these activities.

The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit. In assessing the risk-benefit balance at the time of authorisation, the assumption is made that these benefits and risks apply to the whole target population. However, there may be subsets of patients for whom the risk is greater than that for the target population as a whole, or in whom the benefit may not be as great. In addition, efficacy in the clinical trial setting may not reflect the true effectiveness of the medicinal product in everyday medical practice and so the risk-benefit balance of a medicinal product as assessed at the time of authorisation will inevitably change post-authorisation. Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC include provisions for both post-authorisation safety studies and post-authorisation efficacy studies to be a condition of the marketing authorisation in certain circumstances [REG Art 9(4), Art 10a(1), DIR Art 21a, Art 22a(1)] and for these studies to be included in the risk management plan (RMP) [DIR Art 22c].

Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimisation activities will need to be tailored to the system in place in a particular country or global region. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a medicinal product may also vary between regions. Therefore a product may have different versions of a RMP for each region although there will be core elements which are common to all. For example much of the safety

specification will be the same regardless of where the medicinal product is being used but the epidemiology of the disease may vary between e.g. Africa and Europe, and there may be additional or fewer safety concerns depending upon the target population and indication,

The move to a modular format should facilitate submission to different regulatory authorities. The new modular structure for EU risk management plans will come into force in July 2012 but transitional arrangements whereby either the old or new format can be used, will be put in place and will be posted on the Agency's website¹.

Risk management, is applicable to medicinal products at any point in their lifecycle. However, this module concentrates on peri- and post-authorisation risk management and is applicable to all products regardless of the procedure (centralised, decentralised, mutual recognition or national) leading to authorisation in the EU.

The risks addressed in this guidance are those related to non-clinical and clinical safety. In addition, quality issues may be relevant if they impact on the safety and/or efficacy of the product. Where the disposal of the product might pose a particular risk because of remaining active substance (e.g. patches) this should also be addressed.

Although this module includes the principles of risk minimisation, and details of routine risk minimisation measures, more detail on, in particular, additional risk minimisation tools and the measurement of the effectiveness of risk management can be found in **Module XVI**.

V.B. Structures and processes

V.B.1. Definitions

Identified risk

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

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

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

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include:

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

¹ www.ema.europa.eu

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

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

Important identified risk and important potential risk

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

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

Risk management system

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

Risk management plan

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

Risk minimisation activity (used synonymously with risk minimisation measure)

A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

Safety concern

An important identified risk, important potential risk or important missing information.

Target population (treatment)

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.

V.B.2. Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (including those linked to the Safety Specification section on Missing Information) and their integration, where necessary, in the RMP may enable resources to be used more efficiently and for risks to be put into context. The RMP therefore includes the planning of such studies and is without prejudice to the specific efficacy guidance and measures foreseen in Article 108a of Directive 2001/83/EC.

The principles of risk management are the same regardless of stakeholder or territory (see below).

Figure V.1. The risk management cycle



However, the actions and responsibilities within each step of the cycle will vary according to whether the stakeholder is an applicant/marketing authorisation holder, competent authority, healthcare professional or patient. Other players may be involved in risk-benefit management such as: patient organisations, learned societies, health economists, health authorities, national safety organisations, environmental advisors, occupational health professionals and pharmaceutical distributors but their roles will usually be smaller and complementary to that of the main players.

For applicants/marketing authorisation holders and competent authorities in the EU, there is specific mention of risk management in the legislation. In the EU, as well as complying with the legislation, the primary document and process for risk management adheres to the principles in the **International Conference for Harmonisation (ICH) Guideline E2E on Pharmacovigilance Planning**. Outside of the EU, some territories may have local legislation enshrining either risk management in general or adopting the specific ICH E2E guidance or have developed local guidance. For healthcare professionals, product information, medical treatment guidelines and any materials produced by marketing authorisation holders, competent authority or health authorities will direct prescribing, dispensing, treatment and management of both benefit and risks. For patients, the majority of medicinal products will be prescribed by doctors and dispensed by pharmacists so that management of benefits and risks will

primarily involve complying with treatment schedules and recommendations, being aware of important risks and what actions to take, and reporting to their doctor, pharmacist, and national competent authority any untoward effects. However, in some countries patients may buy medicines directly without guidance from healthcare practitioners so will need to understand the potential benefits and risks of the product and what measures they need to comply with to use the medicine safely and effectively. Whatever the setting, patients who understand the potential benefits and risks of a medicinal product are better equipped to decide whether or not to be treated and to comply with suggested risk minimisation activities.

V.B.3. Responsibilities for risk management within an organisation

The principle organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the competent authorities who regulate them. Within the EU, responsibility for authorisation and supervision of medicinal products is shared between the national competent authorities in Member States, the European Commission and the European Medicines Agency, with the balance of responsibilities depending upon the route of authorisation.

V.B.3.1. Marketing authorisation holders and applicants

In relation to risk management of its medicinal products, an applicant/marketing authorisation holder is responsible for:

- ensuring that it constantly monitors the risks of its medicinal products in compliance with relevant legislation and reports the results of this, as required, to the appropriate competent authorities;
- taking all appropriate actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available;

Other Modules within GVP deal with specific aspects of the above so this Module is confined to the risk management plan and its contents.

ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation. However it was acknowledged at the time of development of ICH-E2E that risk minimisation was an integral part of risk management planning. Details of how the safety specification and pharmacovigilance plan are integrated within the RMP and the detailed structure and format are provided in V.B.5 to V.B.7.

Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorisation applicant/holder who should ensure oversight by someone with the appropriate scientific background within the company.

Further guidance on individual risk minimisation activities is provided in **Module XVI**.

V.B.3.2. Competent authorities

The general responsibilities of competent authorities are discussed in **Module I**. In relation to risk management, the principal responsibilities of competent authorities are:

- constantly monitoring the benefits and risks of medicinal products including assessing the reports submitted by pharmaceutical companies, healthcare professionals, patients and, where appropriate, other sources of information;
- taking appropriate regulatory actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy and completeness of all information produced by the company in relation to its medicinal products;
- ensuring the implementation of risk minimisation activities at a national level;
- effectively communicating with stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, healthcare physicians, patient groups, learned societies etc;
- when necessary, ensuring that marketing authorisation holders of generic and/or similar biological medicinal products make similar changes to their risk minimisation measures when changes are made to those of the the reference medicinal product;
- providing information to other regulatory authorities, this includes notification of any safety activities in relation to a product, including changes to the product information of originator and/or reference medicinal products.

Many of the associated tasks and activities are described elsewhere in GVP and in other scientific guidances. One of the principle tasks of regulatory authorities in relation to risk management is the assessment of risk management plans. The different parts of the RMP need different areas of expertise so ideally assessment of risk management plans should be performed by a multi-disciplinary team. How this can be achieved will depend upon the organisational structure of the competent authority but could include multi-disciplinary meetings or pharmacovigilance experts reviewing RMPs alongside expert assessment reports relating to different sections of the submitted dossier.

V.B.4. Objectives of a risk management plan

As per the Commission Implementing Regulation (EU) No 520/2012, [IR], the RMP must contain the following elements which:

- identify or characterise the safety profile of the medicinal product(s) concerned;
- indicate how to characterise further the safety profile of the medicinal product(s) concerned;
- document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
- document post-authorisation obligations that have been imposed as a condition of the marketing authorisation [IR Art 30].

There is an implicit requirement that to fulfil these obligations a RMP should also:

- describe what is known and not known about the safety profile of the concerned medicinal product(s);

- indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);
- include a description of how the effectiveness of risk minimisation measures will be assessed.

The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. For products requiring periodic safety update reports (PSURs), certain (parts of) modules may be used for both purposes (see V.B.14.).

V.B.5. Structure of the risk management plan

The RMP consists of seven parts. Certain parts of the RMP, in particular the safety specification, are subdivided into modules [IR Annex 1] so the content can be tailored to the specifics of the medicinal product and modules added/removed 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, whilst RMP part III follows the Pharmacovigilance Plan. Differences between indications, formulations and target populations, if several medicinal products have the same active substance, will be similarly accommodated by dividing the relevant parts of the RMP into modules and/or sections. The modular structure also means that the RMP can be updated easily. As the product matures, some RMP modules or sections may cease changing – for example non clinical studies may stop at a certain time as may clinical trials. These RMP modules can be effectively “locked” until new data needs to be added. In addition, certain RMP modules may be omitted in specific circumstances (see [V.C.3.1.](#)).

The Agency will make available on its website a template for the RMP. The submitted RMP should follow the RMP template. The amount of information, particularly in RMP part II, which can be provided will depend on the type of medicinal product and where it is in its lifecycle but this guidance provides an overview of the level of information needed and its format.

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)]. This proportionality can be achieved in three ways: by reducing the number of modules which need to be submitted for products meeting certain conditions (such as well established products/generics see table V.3), and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the important risks and important uncertainties of the product.

An overview of the parts and modules of the RMP is provided below [IR Annex I]:

Figure V.2. Overview of the parts and modules of the RMP

Part I	Product(s) overview
Part II	Safety specification <ul style="list-style-type: none"> 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
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI	Summary of the risk management plan
Part VII	Annexes

Where a RMP concerns more than one medicinal product, a separate RMP part VI must be provided for each medicinal product [IR Art 31].

Information should be provided in enough detail to enable an assessor to understand the issues being presented. Unless specifically mentioned in this guidance, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document that is a scientific synopsis of the relevant parts of the dossier, emphasising the important clinically relevant facts. To aid consistency between the information provided in the CTD and the RMP, the table below indicates the location of information in the CTD is summarised for the RMP:

Table V.1 Mapping between RMP modules and CTD

RMP	CTD
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the target population	Module 2.5 Clinical overview
Module SII Non-clinical part of 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

RMP	CTD
Module SV Post authorisation experience	Module 2.5 Clinical overview - briefly
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post authorisation efficacy studies (including presentation of efficacy data)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

Copies of literature referenced in the RMP should be included in RMP annex 12.

V.B.6. Detailed description of each part of the risk management plan

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

Under Regulation (EC) No 1394/2007², 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 which are not normally a consideration with other medicinal products including risks to living donors, risks of germ line transformation and transmission of vectors. For this reason, for ATMPs, RMP module VII *Identified and potential risks (ATMP)* should replace RMP module VII *Identified and potential risks* as this provides greater flexibility in consideration of the additional risks.

² Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

V.B.7. RMP part I “Product overview”

This should provide the administrative information on the RMP and an overview of the product(s) covered within it.

The information should include:

Active substance information:

- active substance(s);
- pharmacotherapeutic group(s) (ATC code);
- name of marketing authorisation holder or applicant;
- date and country of first authorisation worldwide (if applicable);
- date and country of first launch worldwide (if applicable);
- number of medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

- data lock point of the current RMP;
- date submitted and the version number;
- list of all parts and modules of the RMP with date and version of the RMP when the part/module was last (updated and) submitted.

and

for each medicinal product included in the RMP:

- authorisation procedure (central, mutual recognition, decentralised, national);
- invented name(s) in the European Economic Area (EEA);
- brief description of the product including:
 - chemical class;
 - summary of mode of action;
 - important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- indications:
 - current (if applicable) in the EEA;
 - proposed (if applicable) in the EEA;
- dosage:
 - current (if applicable) in the EEA;
 - proposed (if applicable) in the EEA;
- pharmaceutical forms and strengths:
 - current (if applicable) in the EEA ;
 - proposed (if applicable) in the EEA;

- whether the product is the subject of additional monitoring in the EU.

V.B.8. RMP part II “Safety specification”

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s). It should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used i.e. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine understanding of the risk-benefit profile during the post-authorisation period. In the RMP, the safety specification will form 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.

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

RMP modules SIII–SV form the “Limitations of the human safety database” part of the ICH-E2E safety specification and these, with the addition of RMP modules SI and SVII form the clinical part of the safety specification. RMP modules SVI and the ATMP version of SVII are EU specific although the topics may apply in any territory.

It is recommended that applicants/marketing authorisation holders follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme. Elements which might need to be incorporated include:

- quality aspects if relevant in relation to the safety and efficacy of the product,
- the disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches),
- innovative pharmaceutical forms or
- use with a medical device.

V.B.8.1. RMP module SI “Epidemiology of the indications and target population”

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU of the proposed indication.

Information should be provided on the important co-morbidities in the target population. For example: if a medicinal product is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether 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/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

The RMP should include a statement of the intended purpose and impact of the product e.g. whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease.

V.B.8.2. RMP module SII “Non-clinical part of the safety specification”

This RMP module should present a summary of the important non-clinical safety findings, for example:

- toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- general pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);
- drug interactions;
- other toxicity-related information or data.

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

For other special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

V.B.8.3. RMP module SIII “Clinical trial exposure”

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g.

tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:

- age and gender;
- indication;
- dose;
- racial origin (see also V.B.8.4).

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format.

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

The categories above are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied, and route of administration, number of courses/immunisations or repeat administrations may be important categories to be added.

When presenting age data, categories should be chosen which are relevant to the target population. Broad artificial divisions which are not clinically relevant, such as <65 and >65, should be avoided. Paediatric data should be divided by categories (e.g. ICH-E11); similarly the data on elderly patients should be considered for stratification into categories such as 65-74, 75-84 and 85+, although the age strata should reflect that of the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

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

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

V.B.8.4. RMP module SIV “Populations not studied in clinical trials”

RMP module SIV should discuss which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug. Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these in the overall development programme in relation to the target population should be provided. In discussing differences between target populations and those

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

The implications, with respect to predicting the safety of the product in the marketplace, of any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database with regard to the detection of adverse reactions due to:

1. number of patients studied;
2. cumulative exposure (e.g. specific organ toxicity);
3. long term use (e.g. malignancy);

should be discussed. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

Populations to be considered for discussion should include (but might not be limited to):

- Paediatric population

Children (from birth to 18 years with consideration given to the different age categories as per ICH-E11, or, if justified, to other developmentally meaningful groups i.e. taking into account specific organ maturation). If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- Elderly population

Implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum. The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The cumulative effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular any adverse reactions which might be of special concern in the elderly e.g. dizziness or central nervous system effects should be explored.

- Pregnant or breast-feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast-feeding should be discussed. If the medicinal product is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed. For products where pregnancy should be avoided for safety reasons, , the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medical practice.

- Patients with hepatic impairment

- Patients with renal impairment

- Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)

- Patients with disease severity different from that studied in clinical trials

Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

- Sub-populations carrying known and relevant genetic polymorphism

The extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme has been in patients with a specific mutation, the marketing authorisation holder should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern.

If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and pharmacovigilance plan. Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.

- Patients of different racial and/or ethnic origins

Genetic variants can influence pharmacodynamics and pharmacokinetics, and subsequently affect the efficacy and/or safety of the administered drug. Inter-ethnic differences in drug efficacy and safety have been observed in different ethnic groups due to e.g. genetic polymorphisms.

One example of such inter-ethnic differences is the variation in frequency of the HLA-B*1502 allele. This allele is strongly associated with the occurrence of severe cutaneous adverse reactions to carbamazepine and has a prevalence of about 10% in some Asian populations, whilst the prevalence of the allele is negligible in those of European descent. This is why genomic testing is recommended for patients of some Asian origins when carbamazepine use is planned, while this testing will not make sense for a patient who is of European descent.

Major inter-ethnic differences in pharmacokinetics of drugs may also occur due to types and/or frequencies of gene variants coding for drug metabolising enzymes. The consequences of these inter-ethnic differences could be that the proportion of subjects with particular beneficial effects or adverse reactions varies, leading to different benefit risk profiles and specific recommendations in these ethnic populations.

Furthermore, efficacy in patients may be affected by racial origin. One example is that ACE inhibitors are less potent in black patients of African or Caribbean family origin than in white patients.

Therefore, information on racial origin may be relevant and valuable for evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population.

The experience of drug use in patients with different racial and/or ethnic origins should be discussed including the implications on efficacy and safety, based on pharmacokinetics and pharmacodynamics, in the target population. If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP Part IV. Consideration should also be given as to whether post-authorisation efficacy and/or safety studies are necessary.

V.B.8.5. RMP module SV “Post-authorisation experience”

The purpose of this RMP module is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP module SIV. It should also include brief information on the number of patients included in completed observational studies conducted either to

elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicinal product should also be provided in this module.

V.B.8.5.1. RMP module SV section “Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons”

List any significant regulatory action (including those initiated by the marketing authorisation holder), in any market, taken in relation to a safety concern. Significant regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation. This list should be cumulative, and specify the country, action taken and the date as appropriate. Roll-out in multiple countries of a new safety statement initiated by the MAH can be presented as one action.

When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations as authorised in the EU.

V.B.8.5.2. RMP module SV section “Non-study post-authorisation exposure”

Where marketing of the medicinal product has occurred, the applicant/marketing authorisation holder should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables. These may include age, sex, indication, dose and region (EU versus non EU). Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment. If the data are available, EU use should be broken down into country or sales area.

When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used. Exposure data based on the number of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always used at one dose level for a fixed length of time, which is not the situation with most medicinal products. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used. For example, for medicinal products used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. Competent authorities may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, marketing authorisation holders should consider routinely providing such data where possible.

A more accurate breakdown of drug exposure based on market research should be provided where possible.

If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real world setting, should be provided.

V.B.8.5.3. RMP module SV section “Post-authorisation use in populations not studied in clinical trials”

Where there are data on post-authorisation use in the special populations identified in RMP module SIV as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label. For paediatric use, cross reference may be made to RMP section “Specific paediatric issues” in RMP module SVI (see [V.B.8.6.6.](#)). Information on the safety profile of the medicinal product in these special populations, as compared with the rest of the target population, should also be provided. In particular, any information regarding an increased or decreased benefit in a special population should be provided. Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP module SVII but reference should be made in this section as to which risks and populations are affected.

V.B.8.5.4. RMP module SV section “Post-authorisation off-label use”

Post marketing, updates to the safety specification, should include information on EU off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the authorised product information for a medicinal product . Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU. EU use in clinical trials conducted as part of the marketing authorisation holder’s development programme should be included only in RMP module SIII and not in this section.

Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by national competent authorities for purposes other than risk management. When off label use is a safety concern or a concern has been raised by the competent authorities regarding off-label use, marketing authorisation holders should attempt to quantify such use along with a description of the methods used to arrive at these figures

V.B.8.5.5. RMP module SV section “Epidemiological study exposure”

Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

V.B.8.6. RMP module SVI “Additional EU requirements for the safety specification”

Some safety topics were not included in ICH-E2E but are thought to be of particular interest due to either EU legislation or prior experience of a safety issue.

V.B.8.6.1. RMP module SVI section “Potential for harm from overdose”

Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products 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. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP module SVIII and appropriate risk minimisation proposed in RMP part V.

V.B.8.6.2. RMP module SVI section “Potential for transmission of infectious agents”

The applicant/marketing authorisation holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed. For advanced therapy medicinal products a cross reference to RMP module SVII (ATMP) may be made.

V.B.8.6.3. RMP module SVI section “Potential for misuse for illegal purposes”

The potential for misuse for illegal purposes should be considered. Misuse, as defined in GVP Module VI, refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault. If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the risk minimisation plan.

V.B.8.6.4. RMP module SVI section “Potential for medication errors”

For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They fall broadly into 4 categories:

1. Wrong medication
2. Wrong dose (including strength, form, concentration, amount)
3. Wrong route of administration
4. Wrong patient

Applicants/marketing authorisation holders should consider routinely the likelihood of medication errors. In particular, they should assess, prior to marketing, common sources of medication errors. During the development phase and during the design of a medicinal product for marketing, the applicant needs to take into account potential reasons for medication error. The naming (taking into account the Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed Through the Centralised Procedure³), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered. In

³ See CPMP/328/98 latest version; available on EMA website <http://www.ema.europa.eu>.

addition, the Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use⁴ should be followed.

If a product has potential for serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route. In this situation, medication errors should be included as a safety concern.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.

When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment.

Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design.

If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated RMP and ways of limiting the errors proposed.

If the formulation or strength of a product is being changed, where appropriate, medication error should be included as a safety concern and the measures that the marketing authorisation holder will put in place to reduce confusion between old and new “product” should be discussed in the risk minimisation plan. Similarly, it may be appropriate to discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicinal product.

If the product is to be administered with a medical device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medical device malfunction).

V.B.8.6.5. RMP module SVI section “Potential for off-label use”

The potential for off-label use should be discussed. Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

⁴ See ENTR/F/2/SF/jr (2009)D/89 Eudralex Volume 2C - Regulatory Guidance; available on <http://ec.europa.eu/health/documents/eudralex>

Where appropriate, use could be made of data on actual use versus authorised use in other markets and the implications for the authorisation in the EU discussed.

V.B.8.6.6. RMP module SVI section “Specific paediatric issues”

This section deals with aspects of paediatric use not covered in RMP module SIV.

Issues identified in paediatric investigation plans

Any recommendations for long term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be detailed here. This section should clarify if, and how, this had been taken into account in RMP module SVII. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.

Proposals for specific long term paediatric studies should be considered at the time of application for a paediatric indication and if felt not to be necessary justification should be provided. If an indication in adults precedes an application for paediatric use, any registries established to provide data on use of the product in real medical practice should avoid age related exclusion criteria so that any potential off-label use in the paediatric population can be included.

In some circumstances, the safety concern identified in the paediatric investigation plan may be applicable to the whole population being treated. In these cases, consideration should be given as to whether some of the pharmacovigilance activities and/or risk minimisation activities from the paediatric investigation plan are appropriate for, and should be extended to cover, the whole population. For these safety concerns, this RMP section should also include details of how the specific paediatric aspects will be addressed and all paediatric investigation plan recommendations considered. Cross-reference may be made to RMP modules SIV and SVII and SVII.

Potential for paediatric off-label use

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed. If there are limited treatment options it should not be assumed that clinicians will adhere to the labelled indication so it is important that potential paediatric issues are discussed. Any actual use should be discussed in RMP module SV section “Non-study post-authorisation exposure” (see V.B.8.5.2.) and in RMP module SV section “Post-authorisation use in populations not studied in clinical trials” (see V.B.8.5.3.).

V.B.8.7. RMP module SVII “Identified and potential risks”

This RMP module provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

Because of the need for different additional categories of risks to be considered with advanced therapy medicinal products, a different version of RMP module SVII is available for products classified as advanced medicinal products. Only one version (either sections V.B.8.7.1- V.B.8.7.5 or sections V.B.8.8.1 – V.B.8.8.3) of RMP module SVII should be provided in a RMP.

V.B.8.7.1. RMP module SVII section “Newly identified safety concerns”

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

V.B.8.7.2. RMP module SVII section “Recent study reports with implications for safety concerns”

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (eg RMP module SII; section V.B.8.7.3; V.B.8.7.4; V.B.8.7.5; RMP Module SVI and RMP Module SVIII

V.B.8.7.3. RMP module SVII section “Details of important identified and potential risks from clinical development and post-authorisation experience”

This RMP section should provide more information on the important identified and potential risks. This RMP section should be concise and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the summary of product characteristics (SmPC).

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1). Normally, any risk which is clinically important and which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person’s life, and which could lead to serious consequences if untreated should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

For some products, disposal of the used product may constitute a safety concern, e.g. transdermal patches where there may be significant amounts of active substance remaining in the patch when it is discarded. There may also be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment, e.g. substances which are particularly hazardous to aquatic life which should not be disposed of in landfill sites.

Presentation of risk data:

When the information is available, detailed risk data should include the following:

- frequency;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (i.e. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);

- potential mechanism;
- evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions (in the numerator) and the sales data (in the denominator) is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population and should be avoided. When an accurate frequency is needed for an important identified risk, this should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the medicinal product and the number of patients who experienced the respective identified risk are known.

The denominator should be expressed using the appropriate measure: e.g. number of patients or in patient-time or equivalent units (courses of treatment, prescriptions, etc.) It should be stated clearly which frequency parameter is being used: e.g. incidence proportion (patient units in the denominator) or incidence rate (patient-time units in the denominator). Confidence intervals should be provided. When using patient-time, the underlying assumption is that the hazard function must be nearly constant over the follow-up time. Otherwise it should be split into relevant categories where the assumption of constancy holds. This may be particularly important if treatment duration is a risk factor. Where appropriate, the period of major risk should be identified. Identified risk incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess (relative incidence compared to a specified comparator group) should be given. Time to event data should be summarised using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of an adverse reaction in the presence of competing events.

For potential risks, the background incidence/prevalence in the target population(s) should be provided.

For most RMPs involving single products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns, e.g. accidental IV administration could be a safety concern in a single product with both oral and subcutaneous forms.

For RMPs covering multiple products where there may be significant differences in the identified and potential risks for different products, it may be appropriate to categorise the risks to make it clearer which risks relate to which product. Headings which could be considered include:

- Risks relating to the active substance

This would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of products.
- Risks related to a specific formulation or route of administration

Examples might include an RMP with two products: one a depot intramuscular formulation and the other an oral formulation. Additional concerns relating to accidental intravenous administration clearly would not be applicable to the oral product.
- Risks relating to a specific target population

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

- Risks associated with switch to non-prescription status.

Division of identified and potential risks using headings should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion.

V.B.8.7.4. RMP module SVII section “Identified and potential interactions including food-drug and drug-drug interactions”

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in RMP module SVIII “Summary of the safety concerns.”

V.B.8.7.5. RMP module SVII section “Pharmacological class effects”

Important risks which have not been included in RMP module SVII “Details of important identified and potential risks from clinical development and post-authorisation experience” (above) but which are believed to be common to the pharmacological class should be discussed here. The discussion should include the mechanism, the impact (severity and duration), frequency seen with other members of the same or similar pharmacological class

For risks which have been included in the RMP section SVII “*Details of important and identified and potential risks from clinical development and post-authorisation experience*” above, all that is required in this RMP section are the frequencies seen with the medicinal product compared with those seen with other products in the same or similar pharmacological class.

If there is evidence that a risk, which is common to other members of the pharmacological class, is not thought to be a safety concern with the concerned medicinal product, details, and the evidence supporting this, should be provided and discussed.

V.B.8.8. RMP module SVII “Identified and potential risks (ATMP version)”

Advanced therapy medicinal products (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products (see [Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products](#))⁵. For this reason, for ATMPs, this ATMP specific version of RMP module replaces the standard RMP module SVII.

Although not all of the risks listed in section [V.B.8.8.3](#) are unique to ATMPs or applicable to all ATMPs, they represent the most relevant ones which need to be considered.

V.B.8.8.1. RMP module SVII section “Newly identified safety concerns (ATMP)”

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

⁵ EMEA/149995/2008; available on EMA website <http://www.ema.europa.eu>

V.B.8.8.2. RMP module SVII section “Recent study reports with implications for safety concerns (ATMP)”

Study reports (either interim or final), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (e.g. RMP module SII; section V.B.8.8.3; RMP Module SVI and RMP Module SVIII)

V.B.8.8.3. RMP module SVII section “Details of important identified and potential risks (ATMP)”

This section should provide more information on the most important identified and potential risks. This section should be selective and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the summary of product characteristics (SmPC).

What constitutes an important risk will depend upon several factors including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and is/is likely to be included in the warnings and precautions section of the summary of product characteristics should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of either the patient or donor, affect the quality of life, and which could lead to serious consequences if untreated should also be considered for inclusion. The additional risks specific to ATMPs which should be considered for discussion include:

- 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 results);
- 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, e.g.:
 - 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.8.9. RMP module SVIII “Summary of the safety concerns”

At the end of the safety specification a summary should be provided of the safety concerns. A safety concern may be an:

- important identified risk;
- important potential risk; or
- important missing information.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, similar to the presentation of risks in RMP module SVII, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- safety concerns relating to the active substance;
- safety concerns related to a specific formulation or route of administration;
- safety concerns relating to the target population;
- risks associated with switch to non-prescription status.

Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

V.B.9. RMP Part III “Pharmacovigilance plan”

The purpose of the pharmacovigilance plan is to discuss how the applicant/marketing authorisation holder plans to identify and/or characterise the risks identified in the safety specification. It provides a structured plan for:

- the identification of new safety concerns;
- further characterisation of known safety concerns including elucidation of risk factors;
- the investigation of whether a potential safety concern is real or not;
- how important missing information will be sought.

It does NOT include actions intended to reduce, prevent or mitigate risks

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module SVIII of the safety specification. Early discussions between competent authorities and the marketing authorisation holder or applicant are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all products.

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the applicant/marketing authorisation holder

should list their planned pharmacovigilance activities for that concern. Pharmacovigilance plans should be proportionate to the risks of the product. If routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies) “routine pharmacovigilance” should be entered against the safety concern.

V.B.9.1. RMP part III section “Routine pharmacovigilance activities”

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for pharmacovigilance contained within Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File contains details of the system and processes each marketing authorisation applicant/holder has in place to achieve this. These details are not required to be submitted in the RMP.

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

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

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 adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. Applicants/marketing authorisation holders are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.

Use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine pharmacovigilance.

V.B.9.2. RMP part III section “Additional pharmacovigilance activities”

Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non- interventional studies. A safety concern may have no, or a number of, additional pharmacovigilance activities associated with it depending upon its nature, the degree to which it has already been characterised, and the feasibility of studying it. Applicants/marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long term follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another example, when additional pharmacovigilance activities should be considered, is

when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the “normal” incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a competent authority should be considered.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For important missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer.

Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The applicant/marketing authorisation holder should include all studies designed to address the safety concern or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders, voluntarily, or pursuant to obligations imposed by a competent authority [REG Art 10, Art 10a(1)], DIR Art 21a, Art 22a(1), Art 22c]. Studies requested by other regulatory authorities (including those outside of the EEA) to investigate a specific safety concern should also be included. If a marketing authorisation applicant/holder has a marketing partner, studies designed to address a particular safety concern which are initiated, managed or financed by that partner should be included in the pharmacovigilance plan, if possible.

If, when reviewing a study protocol, a study is thought not to have as its primary focus one of the objectives of a PASS (as described in Module VIII), or a PAES, or the study is judged to be unlikely to achieve its stated scientific purpose, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP.

Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place and recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP)⁶ and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁷. For studies involving children, the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population⁸ should be consulted. It is highly recommended that expert advice is sought on the design and conduct of any studies – whether by the scientific advice procedure or by consulting known experts in the appropriate field. The responsibility for the scientific value of study protocols remains with applicants or marketing authorisation holders, even if they have been previously discussed with competent authorities.

Further guidance on the conduct of post-authorisation safety studies (PASS) is given in Module VIII.

⁶ International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2005; 14 (8): 589-595; available on the ISPE website http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

⁷ ENCePP Guide on Methodological Standards in Pharmacoepidemiology” EMA/95098/2010; available on <http://www.encepp.eu>

⁸ EMEA/CHMP/PhVWP/235910/2005; available on http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000087.jsp&mid=WC0b01ac0580025b90&jsenabled=true

For some safety concerns, additional pharmacovigilance activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or further pre-clinical work. The appropriate guidelines and legislation should be followed in the conduct of these studies.

Protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until completion of the study and submission to the competent authorities of the final study report.

For studies conducted as an obligation, the marketing authorisation holder shall submit the study protocol, in English except for studies to be conducted in only one Member State that requests the study [DIR Art 22a]. For other studies, if the study protocol or the study report is written in another language, the marketing authorisation should facilitate access to study information by including an English translation of the title, the abstract of the study protocol and the abstract of the final study report (see Module VIII.)

Synopses of study reports from additional pharmacovigilance activities should be included in RMP annex 9. The impact of the new data on the benefit-risk profile of the medicinal product should be carefully assessed and the safety specification, pharmacovigilance plan and risk minimisation measures updated accordingly.

V.B.9.2.1. Particular situations with post authorisation safety studies

This section should be read in conjunction with Module VIII – Post authorisation Safety Studies.

a. Studies to measure the effectiveness of risk minimisation measures

Post-authorisation safety studies (PASS) include in their definition studies which measure the effectiveness of risk management measures. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan. Further guidance on measuring the effectiveness of risk minimisation measures can be found in GVP Module XVI

b. Drug utilisation studies

Drug utilisation studies are sometimes requested by national competent authorities to monitor drug usage in their country, often in relation to reimbursement discussions. However, although they may not be initiated to collect safety data, they can provide useful information on whether risk minimisation activities are effective and on the demographics of target populations. Ideally, requests for drug utilisation studies by national competent authorities in one or more EU countries should be identified to the Rapporteur/Reference Member State pre-opinion and included in the pharmacovigilance plan. However, these studies are sometimes requested post-authorisation by authorities not involved in medicinal product licensing. In these circumstances, the studies should be included in the next update to the RMP.

c. Joint studies

If safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a(1), REG Art 10a(1)]. The conduct of a joint study may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. The national competent authority or the Agency should facilitate the agreement of the concerned marketing authorisation holders in developing a single protocol for the study and conducting the study. If, within a reasonable period of time, as determined by the PRAC, the concerned marketing authorisation holders have failed to agree a common protocol, the national competent authority or the Agency, with input from the PRAC, may impose a PASS and define either a common core protocol or key elements

within a protocol which the concerned marketing authorisation holders will have to implement within a timescale laid down within the request. Hence, the study would become a condition of the marketing authorisation and be reflected in the RMP.

In some circumstances, the requirement to do joint studies may relate to a single active substance where there are multiple marketing authorisation holders for the same active substance.

d. Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry)

Registries should ideally include a comparator group so a disease registry will usually be more suitable than a registry confined to a specific product. However, if, an applicant/marketing authorisation holder institutes a registry as part of an agreed RMP, the protocol for the registry will allow all patients who are prescribed the active substance or who have the same disease, as appropriate, to be entered in the registry. Entry to the registry should not be conditional on being prescribed a product with a particular invented name or marketing authorisation holder unless there are clear scientific reasons for this. The same applies to similar biological products.

Unless there are over-riding public health or scientific concerns which lead to mandatory inclusion in a registry, refusal to enter a registry should not normally be a reason for refusing access to a medicine.

V.B.9.3. RMP part III section “Action plans for safety concerns with additional pharmacovigilance requirements”

For safety concerns with additional pharmacovigilance activities only, the action plan for each safety concern should be presented according to the following structure:

- safety concern;
- proposed action(s);
- individual objectives of proposed action(s) (ie what aspects of the safety concern they are intended to characterise);

For each action:

- details of individual action
 - steps
 - milestones (including expected dates)

As well as listing any additional pharmacovigilance activities under “proposed actions,” protocols (draft or otherwise) for any formal studies should be provided in RMP annex 6. Marketing authorisation applicants/holders should also follow the requirements detailed in Module VIII, where appropriate. It is recommended that the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁹ including the ENCePP Checklist for Study Protocols¹⁰, should be referred to when considering epidemiological protocol design.

⁹ ENCePP Guide on Methodological Standards in Pharmacoepidemiology” EMA/95098/2010; available on <http://www.encepp.eu>

¹⁰ ENCePP Checklist for Study Protocols”, EMEA/540136/2009; available on <http://www.encepp.eu>

V.B.9.4. RMP part III section “Summary table of additional pharmacovigilance activities”

The pharmacovigilance plan describes pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions of the marketing authorisation (MA) either because they are key to the benefit-risk of the product, or because they are specific obligations in the context of a MA under exceptional circumstances. If the obligation is a non-interventional PASS, it will be subject to the supervision as described in Art 107 (m)-(q) and the format and content as specified in the EC implementing measures.

The pharmacovigilance plan also includes studies that are conducted or financed by the marketing authorisation holder to address particular safety concerns and so includes studies which are not obligations in the above sense. These studies may be on-going or planned, may have been requested by another regulatory authority, may have been specifically requested by the CHMP or may have been suggested by the marketing authorisation applicant/holder and agreed with the CHMP as forming part of the pharmacovigilance plan. They may also be conducted to evaluate the effectiveness of risk minimisation activities.

Finally, the Pharmacovigilance Plan also has a role in providing an overview of studies which, although not part of the formal agreed plan to identify and characterise specific safety concerns, the Rapporteur, Reference Member State or national competent authority needs to be aware of. These studies are typically requested post-authorisation by a national competent authority for reimbursement reasons e.g. drug utilisation studies.

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, i.e.:

- 1) Imposed obligations in the meaning of Art. 10/10a and 21a/22a included as a condition of the MA
- 2) Specific Obligations in the framework of a MA under exceptional circumstances. These studies will also be reflected in Annex II to the marketing authorisation (or national equivalent).
- 3) Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities
- 4) Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities.

Table V.2: Attributes of different PhV activities

	Type of activity	In Annex II of Opinion (CAPs only)	Category in Summary table of PhV activities	Status	Supervised under Article 107m	Supervised under Article 107 n-q
Imposed PASS	"Interventional"*	X	1	Mandatory and subject to penalties		
	Non-interventional	X	1	Mandatory and subject to penalties	X	X
Specific obligation	"Interventional"*	X	2	Mandatory and subject to penalties		
	Non-interventional	X	2	Mandatory and subject to penalties	X	X
Required	"interventional"*		3	Legally enforceable		
	Non-interventional		3	Legally enforceable	X	
Stated	"interventional"*		4	Not enforced		
	Non-interventional		4	Not enforced	X	

*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.

For activities in categories 1-3, the following summary table should be used:

Description of Activity	Milestones <i>(may be several per activity)</i>	Due Date <i>(may be several per activity)</i>

For activities in category 4 the following summary table should be used:

Description of Activity	Expected date when results will be available

V.B.10. RMP part IV “Plans for post-authorisation efficacy studies”

Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months – 3 years). The benefit (efficacy of the medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.

For many medicines there will not be a need for post-authorisation efficacy studies. However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorisation is necessary.

The regulations on paediatric medicinal products (Regulation (EC) No 1901/2006)¹¹, and advanced therapy medicinal products (Regulation (EC) No 1394/2007)¹² provide the legal basis and 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.

In addition, article 10a(1) of Regulation (EC) No 726/2004 and article 21a(f) and article 22a(1) of Directive 2001/83/EC, provide the legal basis for requiring post-authorisation efficacy studies for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision. Although the legislation refers to the studies as post-authorisation efficacy studies, the fact that these efficacy issues can only be resolved post-authorisation implies that this term includes effectiveness studies.

The requirement for efficacy studies post authorisation refers solely to the current indication(s) and not to studies investigating additional indications.

¹¹ Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

¹² Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

V.B.10.1. RMP part IV section “Summary of existing efficacy data”

As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicinal product, the information should be provided by medicinal product to permit easy extraction for the summary of the RMP module. Similarly medicinal products with more than one indication should have a separate summary of efficacy for each one.

The summary of efficacy (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

- current (gold) standards of treatment
- where the medicinal product fits in the therapeutic armamentarium (ie 1st line, relapse etc)
- a brief statement of the standard against which the medicine was judged
- number of patients in pivotal studies and treatment regimes
- results in lay language

The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

- the robustness of the endpoints on which the efficacy evaluation is based
- applicability of the efficacy data to all patients in the target population;
- factors which might affect the efficacy of the product in everyday medical practice;
- variability in benefits of treatment for sub populations.

For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact on the benefits of the medicinal product discussed.

V.B.10.2 Tables of post-authorisation efficacy studies

A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex 8.

Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should also be included in this part of the RMP.

It should be noted that the Commission may adopt a delegated act on the situations where efficacy studies may be required and the Agency shall adopt scientific guidance on efficacy studies.

Efficacy studies which are specific obligations and/or conditions of the MA

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

Other efficacy/effectiveness studies

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

V.B.11. RMP Part V “Risk minimisation measures”

On the basis of the safety specification, a marketing authorisation applicant/holder should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns. It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

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. Examples when multiple risk minimisation plans could be considered include:

- an active substance where there are products with both prescription only and non-prescription legal status;
- medicinal products where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example an active substance which causes important QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;
- active substances where there are major risks which differ according to the target population.

Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally authorised product labelling) or additional risk minimisation activities (e.g. Dear Healthcare Professional Communications/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

All risk minimisation measures should be reviewed at regular intervals and their effectiveness assessed (see V.B.11.4).

Additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures in general is discussed in more detail in [Module XVI](#).

V.B.11.1. RMP part V section “Routine risk minimisation”

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

- the summary of product characteristics;
- the labelling;
- the package leaflet;
- the pack size(s);
- the legal status of the product.

The summary of product characteristics (SmPC) and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal product. The [Guideline on Summary of Product Characteristics](#)¹³ provides guidance on how information should be presented. As discussed in [V.B.8.6.4.](#), the design of the packaging, and even the formulation itself, may play an important role in preventing medication error.

a. 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: 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 is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

b. Legal status

All medicinal products in the EU have a 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 the conditions under which a patient may receive a medicinal product.

When a marketing authorisation is granted, it 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. The conditions under which a medicinal product is made available is commonly referred to as the “legal status” of a medicinal product. Typically it

¹³ http://ec.europa.eu/health/files/eudralex/vol-2/c/smcp_guideline_rev2_en.pdf

includes information on whether or not the medicinal product is subject to medicinal prescription. It may also restrict where the medicinal product can be administered (e.g. in a hospital, but see below) or by whom it may be prescribed (e.g. specialist).

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

Restricted medical prescription

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

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
- the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere; or
- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment [DIR Art 71(3)].

In the case of an application for a marketing authorisation submitted in accordance with the centralised procedure, the CHMP is responsible for recommending the legal status to the Commission. Although the use of legal status is not an activity that can be used directly by a marketing authorisation applicant for the purposes of risk reduction, the marketing authorisation applicant could request the competent authority to consider a particular legal status and this is indicated in the SmPC.

However, the definition of what constitutes a specialist is not uniform throughout the Member States so, in practice, the term “specialist” is usually phrased in section 4.2 of the summary of product characteristics (SmPC) as: “treatment by a physician experienced in the treatment of <the disease>”. Although restricting to use in a hospital environment may in practice ensure that the medicinal product is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicinal product can be safely administered. For example the term “clinic” has different connotations depending upon the country. For this reason, the type of equipment needed should be specified rather than a location: e.g. “use in a setting where resuscitation equipment is available.”

Special medical prescription

For classification as subject to special medical prescription, the following factors shall be taken into account:

- 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; or
- 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 previous indent as a precautionary measure [DIR Art 71(2)].

Categorisation at Member State level

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

The majority of safety concerns may be adequately addressed by routine risk minimisation activities. However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary.

V.B.11.2. RMP part V section “Additional risk minimisation activities”

Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

Many additional risk minimisation tools are based on communication which aims to augment the information in the summary of product characteristics (SmPC) and the package leaflet. Any communication material should be clearly focused on the risk minimisation goals, and should not be confused or combined with promotional material for marketing campaigns. Further description and guidance on the use of additional risk minimisation activities is provided in **Module XVI**.

It is essential that appropriate specialists/ experts are involved when developing risk minimisation activities. Marketing authorisation applicants/ holders are also encouraged to discuss risk minimisation plans with the competent authorities as early as is feasible when it is likely that specific risk minimisation activities will need to be adapted to the different health care systems in place in the different Member States. For very complex risk minimisation measures, it may be appropriate to contact competent authorities, in the countries where it is planned to market the product, either prior to submitting risk minimisation proposals or during the course of the evaluation procedure. Where possible and appropriate, proposed risk minimisation activities should be discussed with patients and healthcare professionals if it is likely that risk minimisation activities will be directed towards them.

The Pharmacovigilance Risk Assessment Committee (PRAC) is the body mandated to review RMPs and make recommendations on their content and on the suitability of proposed pharmacovigilance activities and risk minimisation measures. For centrally authorised products, only additional risk minimisation measures which are recommended by the PRAC and subsequently agreed by the CHMP will be allowed in the risk minimisation plan and any other activities considered as not essential for the safe and effective use of the product will need to be removed and an updated RMP submitted before the CHMP Opinion. Additional risk minimisation activities will become, once agreed by the European Commission, conditions of the marketing authorisation and the key elements will be detailed in annex II and annex 127a of the CHMP Opinion as appropriate. Where appropriate, full details of additional risk minimisation activities (including mock ups) should be provided in RMP annexes 10 and 11.

Educational material

Any educational material should be non-promotional. It is recommended that communication experts, patients and healthcare professionals are consulted on the design and wording of educational material and that, where appropriate, it is piloted before releasing for use.

For centrally authorised products, the CHMP will agree the key elements of what should be included in the educational material and these key elements will become, once agreed by the European Commission, a condition of the marketing authorisation. The final version of the educational material will need to be approved by the national competent authority for the territory in which it will be used who will check that the material contains the key elements in an appropriate design and format and is not promotional.

For public health reasons, applicants/marketing authorisation holders for the same active substance may be required by the competent authority to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorisation applicants/holder are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material

Further extensive guidance on additional risk minimisation measures is provided in [Module XVI](#).

V.B.11.3. Format of risk minimisation plan(s)

Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed then "none proposed" should be entered against the objective.

For each safety concern, the following information should be provided:

- Objectives of the risk minimisation activities
- routine risk minimisation activities;
- additional risk minimisation activities (if any), individual objectives and justification of why needed;
- how the effectiveness of each (or all) risk minimisation activities will be evaluated in terms of attainment of their stated objectives;
- what the target is for risk minimisation, i.e. what are the criteria for judging success;
- milestones for evaluation and reporting.

For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC), or a précis, should be provided along with details of any other routine risk minimisation activities proposed for that safety concern. If the medicinal product has two or more marketing authorisations (ie in different Member States) which have different SmPC text, it may be appropriate to comment on the differences in the text between member states.

V.B.11.4. RMP part V section "Evaluation of the effectiveness of risk minimisation activities"

Risk minimisation measures are public health interventions intended to prevent or reduce the probability of the occurrence of adverse reactions associated with exposure to a medicinal product, or to reduce their severity/impact on the patient should the adverse reactions occur. The terms "risk minimisation measures and risk minimisation activities are used virtually synonymously in GVP. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout

the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall benefit-risk profile is optimised.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable. Such information may be presented by region, if applicable/relevant. Results of any studies to assess the impact or other formal assessment(s) of 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 alternative activities need to be put in place. The marketing authorisation holder should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

In certain cases it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks.

More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in [Module XVI](#).

V.B.11.5. RMP part V section “ Summary of risk minimisation measures”

A table summarising the routine and additional risk minimisation activities by safety concern should be provided. This table will be used in the EPAR.

V.B.12. RMP part VI “Summary of activities in the risk management plan by medicinal product”

A summary of the RMP for each medicinal product shall be made publically available [REG Art 23(3), Art 26(c), DIR Art 106(c) IR Art 31(2)]. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information [IR Art 31(1)].

It is difficult for one summary to satisfy the needs of all stakeholders and there may be a need for a summary of the RMP to be provided for different stakeholders in varying formats. For products authorised under the centralised procedure, the European Medicines Agency currently publishes a full scientific assessment of the dossier in the format of a European Public Assessment Report (EPAR). This contains a summary of the RMP in an abbreviated tabular format since much of the relevant safety and efficacy data is contained elsewhere within the EPAR. The Agency also publishes a brief summary of the EPAR written in lay language.

For all products there needs to be

A scientific summary of the RMP written for the lay reader to fulfil the requirements of the above articles and principles of transparency in the legislation. This will be known as “the summary of the RMP” and is described in sections V.B.12.1 – V.B.12.7. This shall be provided for all

medicinal products which have a RMP regardless of whether they are centrally or nationally authorised.

The Summary of the RMP shall be written by the MAA/MAH and will be evaluated during the assessment of the RMP. The final format of the Summary and processes for its production and publication are still subject to discussion. Further details will be published on the Agency website and those of national competent authorities (as appropriate) as soon as these are available.

In addition:

Depending upon the format, and whether, a public assessment report is published there may also be a requirement for additional summaries of the RMP to be provided for inclusion in these documents.

For centrally authorised products, in addition to “the summary of the RMP” intended for the lay reader, summary tables of the RMP showing the safety concerns, the pharmacovigilance plan, plans for post-authorisation efficacy and risk minimisation measures will be included in the European Public Assessment Report (EPAR). In addition, a brief statement on the risk management plan will be included in the “Summary of the EPAR.”

Further details of requirements and formats will be published on the Agency website and those of national competent authorities (as appropriate) once discussions are finalised.

V.B.12.1. RMP part VI section “format and content of the summary of the RMP”

This is a scientific summary, written for the lay reader to fulfil the requirements in the legislation. To present a balanced picture, the risks discussed in the RMP should be put into context with the benefits of the medicinal product. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

The summary of the RMP part VI should contain the following information based on RMP modules SI, SVIII and RMP parts IV and V:

For each indication:

- Overview of disease epidemiology
- Summary of existing efficacy data

For the medicinal product

- Summary of safety concerns
 - Important identified risks
 - Important potential risks
 - Important missing information
- Summary of risk minimisation activities by safety concern
- Planned post authorisation development plan

- Studies which are a condition of the marketing authorisation (see sections V.B.9.4 and V.B.10.2)
- Major Changes to the Risk Management Plan over time

V.B.12.2. RMP part VI section “Overview of disease epidemiology”

The applicant/marketing authorisation holder should summarise the epidemiology of the disease/condition the medicinal product is intended to treat or prevent (as presented in RMP module SI) in a non-alarmist manner and in language appropriate to the target population.

If the product is used in a range of disease severity, this fact should be emphasised and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy. If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5 year survival) figures relate to historical treatment.

If the product is a diagnostic, product used for anaesthesia or similar usage not associated with a particular disease/condition then this section of the overview may be omitted.

V.B.12.3. RMP part VI section “Summary of existing efficacy data”

Cross link/reference to V.B.10.1. RMP part IV section “Summary of existing efficacy data”

V.B.12.4. RMP part VI section “Summary of safety concerns”

This section should briefly describe the safety concerns in suitable language for the general public. It should include the frequency and severity of the safety concern for the important identified risks and their preventability.

Risk	What is known	Preventability
Risk 1		
Risk 2 etc		

For important potential risks the reasons why the reason why it is thought to be a potential risk (e.g. toxicology in animal study, known effect in other members of the pharmaceutical class) should be explained together with the uncertainties, e.g. “occurs in other medicinal products in the same class but was not seen in the clinical trials for this medicinal product which studied 3,761 people”.

Risk	What is known
Risk 1	
Risk 2 etc	

For important missing information it should be stated (using the above format as well) that it hasn't been studied, the relevance to the target population and what the recommendations are, e.g. contraindication, use with caution etc.

V.B.12.5. RMP part VI section “Summary of risk minimisation activities by safety concern”

Details of routine risk minimisation measures will be provided in the published summary by a link to the product information.

For each safety concern which has additional risk minimisation measures, brief details of the measures for that concern should be provided. The objective and rationale for each measure should be stated along with the proposed actions e.g.:

These additional risk minimisation measures are for the following risks:

Blood clots (Thromboembolic events)

Healthcare Professional and patient education

Objective and rationale
Patients and HCPs to understand the risk of occurrence of thromboembolic events and the appropriate management of this risk.

Proposed actions

- HCP educational materials to be provided to prescribing physicians and pharmacists warning about these risks and measures to take

- Patient booklet will inform patients what the symptoms of thromboembolic events are and the importance of seeking medical help immediately

- Direct HCP communication prior to launch ('Dear HCP' letter).

Where there are safety concerns specific to a particular indication or population, or where an ATMP is involved it may be appropriate to structure the risks by the headings suggested in module SVII

V.B.12.6. RMP part VI section “Planned post-authorisation development plan”

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from sections V.B.9.4. and V.B.10.2. Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

List of studies in post authorisation development plan

Study	Objectives	Safety concerns/efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study 1				
Study 2 etc				

Studies which are a condition of the marketing authorisation

Statement on which studies in the above table are conditions of the MA e.g. "None of the above studies is a condition of the marketing authorisation."

V.B.12.7. RMP part VI section "Summary of changes to the risk management plan over time"

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date and version number of the RMP when new safety concerns were added or existing ones removed or changed, dates and version of the RMP when new studies were added or finished, and a brief summary of changes to risk minimisation activities and the associated dates these changes were agreed. Since changes to risk minimisation activities involve a variation, the date used for changes to risk minimisation activities should be that of the decision, whether by the European Commission or a national competent authority. The date for safety concerns and studies should be the date of the RMP in which they are first added.

V.B.13. RMP part VII "Annexes to the risk management"

The RMP should contain the annexes listed below. Annexes 1-3, 10 and 11 should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing issues in both parts III and IV of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

RMP annex 1: Interface between RMP and Eudravigilance/EPITT

(electronic only)

See <http://eudravigilance.ema.europa.eu/human/EURiskManagementPlans.asp>

RMP annex 2: Current (or proposed if product is not authorised) local (centralised/mutual recognition/decentralised/national) summary of product characteristics (SmPC) and package leaflet. If multiple versions are included, they should show in which Member State(s) they are applicable. If available, a core SmPC should be provided with an overview of the changes applicable to the SmPC in each Member State

RMP annex 3: worldwide marketing authorisation status by country (including EEA). This should include:

- current licence status (approved/refused/ under review/ suspended/expired/withdrawn)
- date(s) of approval/refusal/suspension/expiration/withdrawal,
- date(s) marketed/withdrawn from market
- trade name(s)
- any explanatory comments.

RMP annex 4:	Synopsis of on-going and completed clinical trial programme
RMP annex 5:	Synopsis of on-going and completed pharmacoepidemiological study programme
RMP annex 6:	Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III
RMP annex 7:	Specific adverse event follow-up forms
RMP annex 8:	Protocols for proposed and on-going studies in RMP part IV
RMP annex 9:	Synopsis of newly available study reports for RMP parts III-IV
RMP annex 10:	Details of proposed additional risk minimisation activities (if applicable)
RMP annex 11:	Mock up examples in English (or the National language if the product is only authorised in a single Member State) of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisations including those using the mutual recognition or decentralised procedure as applicable.
RMP annex 12:	Other supporting data (including referenced material)

V.B.14. The relationship between the risk management plan and the periodic safety update report

The primary post-authorisation pharmacovigilance documents will be the RMP and the periodic safety update report (PSUR). Although there is some overlap between the documents, the main objectives of the two are different and the situations when they are required are not always the same. Regarding objectives, the main purpose of the PSUR is integrated, post-authorisation risk benefit assessment whilst that of the RMP is pre-and post-authorisation risk-benefit management and planning. As such the two documents are complementary. Regarding submission, whereas for many medicinal products, both documents will need to be submitted, for other medicinal products only one will be required depending upon where the product is in its lifecycle. For this reason both documents need to be "stand-alone" but it is anticipated that certain modules may be common to prevent duplication of effort.

The PSUR examines the overall safety profile as part of an integrated benefit-risk evaluation of the medicinal product at set time periods and as such will consider the overall benefit risk profile of the medicinal product (and a much wider range of (suspected) adverse reactions). It is anticipated that only a small proportion of these would be classified as important identified or important potential risks

and become a safety concern discussed within the RMP. Deciding to add an adverse reaction to section 4.8 of the summary of product characteristics (SmPC) is not a sufficient cause per se to include it as a safety concern in the RMP (see [V.B.8.7.2.](#)).

When a PSUR and a RMP are to be 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, this risk should be included as a safety concern 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.14.1. Common modules between periodic safety update report and risk management plan

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

Table V.3: Common sections between RMP and PSUR (may not be in identical format)

RMP section	PSUR section
Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”	Section 3 – “Actions taken in the reporting interval for safety reasons”
Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation exposure”	Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”
Part II, Module SVII – “Identified and potential risks”	Sub-section 16.4 – “Characterisation of risks”
Part II, module SVIII – “Summary of the safety concerns” (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)	Sub-section 16.1 – “Summary of safety concerns”
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.15. Principles for assessment of risk management plans

The principle points which need to be considered when preparing or reviewing a risk management plan for a medicinal product are:

a. 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 from other sections of the dossier 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 addressed under ICH-E2E, e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error etc?
- Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and important 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?
- Does its place in the therapeutic armamentarium as described concur with the intended indication and current medical practice?

b. 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 which have been imposed by a competent authority as conditions clearly identified?
- If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
- Are the proposed additional studies necessary and/or useful?
- When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
- Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

c. Plans for post-authorisation studies on efficacy

- Does the description of the efficacy of the product and what studies and endpoints it was based on conform with the contents of the dossier?
- Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product)?

d. Risk minimisation measures

- Does the product information adequately reflect all important identified risks and important missing information?

- Are any potential risks sufficiently relevant to the safe and effective use of the product that information about them should be included in the product information?
- Is the proposed wording about the risks and location in the product information appropriate and in line with relevant guidelines (e.g. SmPC guideline)?
- Has the marketing authorisation holder considered ways to reduce medication errors?
- Has this been translated into appropriate product information (including device design where appropriate) and pack design?
- Are proposed risk minimisation activities appropriate and adequate?
- Have additional risk minimisation activities been suggested and if so, are they risk proportionate and adequately justified?
- Are the methodologies for measuring and assessing 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?

e. Summary of the Risk Management Plan

- Is it a true representation of the RMP?
- Have the facts been presented appropriately
- Is the content, format and language suitable for the intended audience?
- Have all required formats been provided?

f. When an update is being assessed

- Have new data been incorporated into the safety specification?
- 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?
- Does the new data suggest that a formal evaluation of the risk-benefit balance (if not already done in a PSUR) is needed?

V.B.16. 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 **Module I**. The marketing authorisation holder should maintain records of when RMPs were submitted to EU competent authorities and the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by appropriately qualified pharmacovigilance inspectors.

V.C. Operation of the EU network

Risk management in the EU has historically focused upon the risk reduction approach. In the EU, the legislation uses the terms “risk management system” and “risk management plan.” The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit.

V.C.1. Legal basis for the implementation of risk management within the EU

Directive 2001/83/EC and Regulation (EC) No 726/2004 as amended contain many requirements in relation to pharmacovigilance and in particular risk management. The following articles provide the main references in relation to the legal basis for risk management but additional articles may also be relevant.

Directive 2001/83/EC

Article 8 (3), Article 21a, Article 22a, Article 22c, Article 104, Article 106(c), Article 127a

Commission Implementing Regulation (EU) No. 520/512

Article 30, Article 31, Article 32, Articles 33, Annex 1

Regulation (EC) No 726/2004

Article 6, Article 9(4), Article 10a, Articles 23(3), Article 26(c)

Regulation (EC) No 1901/2006

Article 34

Regulation (EC) No 1394/2007

Article 14

V.C.2. Risk management in the EU

As stated above, the overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. Therefore, although the legal provisions primarily relate to risks, public health will be better served by looking at both benefits and risks. Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC, which apply from July 2012, include provisions for post-authorisation efficacy studies, in addition to post-authorisation safety studies, to be a condition of the marketing authorisation in certain circumstances.

The requirements in the Directive and Regulation are linked to medicinal products. However, to prevent duplication of planning and resource utilisation, the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC provides the possibility for risk management plans to be substance specific. For an individual marketing authorisation holder and applicant, all products containing the same active substance should be included in one RMP [IR Art 30(2)] unless separate presentations are requested by the competent authority or agreed by the same at the request of the applicant/marketing authorisation holder. If the marketing authorisation holder has products in the same substance class

authorised under different authorisation routes (i.e. centralised, decentralised), the competent authorities should be notified of this fact and the need for separate RMPs discussed with them. Pragmatic and practical considerations should determine the need for united or separated RMPs.

V.C.3. Situations when a risk management plan should be submitted

An RMP or an update, as applicable, may need to be submitted at any time during a product's life-cycle, i.e. during both the pre- and post-authorisation phases.

Article 8(3)(iaa) requires that for all new marketing applications: the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned shall be submitted, together with a summary thereof.

Situations, in addition, where a RMP or RMP update will normally be expected include:

- with an application involving a significant change to an existing marketing authorisation:
 - new dosage form;
 - new route of administration;
 - new manufacturing process of a biotechnologically-derived product;
 - paediatric indication;
 - other significant change in indication;

A significant change in indication is a change of authorised indication(s) of a medicinal product where the new treatment target population differs materially from the one for which the medicinal product was previously authorised. This includes (but is not limited to): a new disease area, a new age group (e.g. paediatric indication) or a move from severe disease to a less severely affected population. It may also include a move from 2nd line or other therapy or for an oncology product a change to the concomitant medication specified in the indication.

- at the request of the Agency or national competent authority when there is a concern about a risk affecting the risk-benefit balance;
- at the time of the renewal of the marketing authorisation if the product has an existing risk management plan.

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

An updated RMP should always be submitted if there is a significant change to the benefit-risk balance of one or more medicinal products included in the RMP

V.C.3.1. Requirements in specific situations

Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted (see Figure V.3) unless otherwise requested by the competent authority. However, any safety concerns identified in a reference medicinal product in a module which is omitted from the risk management plan of a generic should be included in RMP module SVIII unless clearly no longer relevant.

a. New applications involving generic medicinal products

For new applications under Article 10(1) of Directive 2001/83/EC, RMP modules SI – SVII may be omitted. RMP module SVIII should be based on the safety concerns of the reference medicinal product unless the generic differs significantly in properties which could relate to safety, or unless requested otherwise by the Agency or national competent authority. Provided the reference medicinal product does not have any additional pharmacovigilance activities or efficacy studies imposed as a condition of the marketing authorisation, RMP parts III and IV may be omitted. Part VI should be based on an appropriately modified version of the public summary of the reference medicinal product.

Further guidance will be provided for situations where the reference medicinal product does not have a RMP.

For updates to the RMP, RMP module SV should be included.

b. New applications under Article 10c “informed consent”

For new applications under Article 10c of Directive 2001/83/EC, the RMP should be the same as the RMP of the cross-referred medicinal product. A RMP will still be required even if the cross-referred product does not have a RMP.

c. New applications involving hybrid or fixed combination medicinal products

For new applications under Article 10(3) or Article 10b of Directive 2001/83/EC, only the data on the fixed combination or data relating to the differences compared with the reference medicinal product need be supplied for RMP modules SII and SIII.

d. New applications under Article 10a “well established medicinal use”

For new applications under Article 10a of Directive 2001/83/EC, RMP modules SII - SIV may be omitted.

e. New applications for a product with new indications where the marketing authorisation applicant already has products with the same active substance authorised for 10 years

When an application for a new medicinal product, is for the same active substance for which the marketing authorisation applicant already has one or more existing authorised and marketed product(s) and

1. the provisions of “well established medicinal use” cannot be met; and
2. the marketing authorisation applicant does not have a risk management plan for any product containing the active substance; and
3. the currently authorised products were placed on the market in the EU 10 or more years prior to the application.

Clinical trial data relating to the already authorised product(s) may be omitted from RMP module SIII and RMP module SIV should be written only in reference to the target population(s) of the new application unless requested otherwise by the competent authority. However, data from experience of the use of the already authorised medicinal products in the special populations which are the subject of RMP module SIV may be included.

Figure V.3. Requirements for new marketing applications

Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Well established use"	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Application under Article 10(c) of Directive 2001/83/EC

^ May be omitted under certain circumstances

* Modified requirement

f. Initial risk management plan for medicinal products on the market in the EU for 10 years

Unless otherwise requested by the Agency or competent authority, marketing authorisation holders required to submit an initial RMP for a marketed product may omit modules SIII and SIV provided the following conditions are met:

1. the product was placed on the market 10 or more years before the requirement for an RMP is established; and
2. the requirement for an RMP is not due to an application for a significant change to an existing marketing authorisation.

If condition 2 cannot be met, clinical trial data relating to this change should be supplied in RMP module SIII but RMP module SIV may be omitted. Discussion of the existing post-authorisation data and its applicability to the target population should be extensively discussed in RMP module SV.

V.C.4. Submission of the risk management plan

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

The Agency is charged with setting up and maintaining a repository for PSURs in collaboration with competent authorities in Member States and the European Commission (see **Module VII**). It is anticipated that this will contain an RMP module. In the interim period, details of submission

requirements and the electronic format will be provided on the Agency and Member State websites as appropriate.

V.C.5. Updates to the risk management plan

If an RMP has previously been submitted by the applicant/marketing authorisation holder for the active substance, any following submissions shall be in the form of an update unless requested otherwise. Each submission of the RMP shall have a distinct version number and shall be dated. This applies whether the entire RMP or only a part or module is being submitted [IR Art 32(2)]. When technically feasible, clean and track change versions should be submitted along with a cover letter detailing the changes since the last submitted version.

The time schedule for providing “routine” updates to the RMP will normally be included as a condition of the marketing authorisation, or otherwise notified to the MAH by the competent authority. It is anticipated that, where a PSUR is also required, the timing for submission of the RMP would be aligned with that of PSUR updates. These are the maximum times between updates and do not remove the responsibility of the marketing authorisation holder to monitor the safety profile of the products nor the requirement for an updated RMP to be submitted if there is a significant change to the benefit-risk profile of one or more medicinal products included in the RMP.

If there has been no change to the RMP since the previous submission (i.e. if a “routine” update is due shortly after the end of a procedure), the marketing authorisation holder may submit a letter explaining that there is no change and not submit an RMP update.

Unless specified otherwise, when both PSURs and RMPs are required for a product, routine updates to the RMP should be submitted at the same time as the PSUR.

If the requirement for providing routine updates to the RMP is not specified as part of the marketing authorisation, routine updates should be provided (unless requested otherwise by the competent authority):

- annually until the first renewal of the marketing authorisation
- every three years thereafter.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable (see [V.B.11.4.](#)).

For medicinal products which have an existing RMP in a format different to that introduced in this guidance, the Agency will publish on its website a timescale by when updates to the RMP should be in the new format.

V.C.5.1. Updates to the risk management plan submitted during a procedure

A medicinal product can only have one “current” version of a RMP. If a medicinal product has more than one procedure in process at the same time which requires submission of a RMP a combined RMP should be submitted with appropriate separation of data in RMP module SIII.

If several updates to the RMP are submitted during the course of a procedure, the version considered as the “current” RMP for future updates and track changes purposes, shall be the last one submitted before the Opinion. For example, in the final weeks before the Opinion, the RMP may be updated several times to reflect on-going PRAC and CHMP discussions, e.g. changed indications, changes in SmPC wording which affect risk minimisation.

Following the finalisation of the procedure, the final version of the RMP should be provided in eCTD. The RMP should reflect the outcome of the procedure – ie removal of all references and data which were subject to a negative Opinion. The exception to this requirement is that populations studied in clinical trials related to a negative Opinion may be included in suitably annotated exposure data in RMP module SIII.

Unless requested otherwise, for RMPs updated during (after the start) of a procedure, track changes should show changes since the start of the procedure whilst the cover letter should show changes since the last version was submitted.

If there is an ongoing procedure for which an RMP has been submitted, “routine” updates should not be submitted during the procedure.

V.C.6. Procedure for the assessment of the risk management plan within the EU

Within the EU, the regulatory oversight of RMPs for products authorised either centrally or in more than one Member State lies with the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC appoints a PRAC rapporteur for an individual RMP who works closely with the (Co-)Rapporteur(s) appointed by the CHMP or with the Reference Member State. Further guidance on the details of the process will be added later.

The EMA may, on a case-by-case basis, consult with healthcare professionals and patients during the assessment of RMPs to gather their input on proposed risk minimisation measures.

V.C.7. Implementation of additional risk minimisation activities for centrally authorised products

Centrally authorised products have one marketing authorisation for the whole of the EU. However, individual Member States may have very different health systems and medical practice may differ between Member States so the conditions and restrictions in the marketing authorisation may be implemented in different ways depending upon national customs. For this reason there will be two Commission Decisions – one addressed to the marketing authorisation holder describing the key elements of any conditions and/or restrictions that the marketing authorisation holder must implement, and one addressed to the Member States giving the Member States the responsibility for ensuring that the key elements described in the conditions and/or restrictions are implemented by the marketing authorisation holder in their territory. How these key elements are implemented in each Member State is a matter for discussion and agreement between the national competent authority and the marketing authorisation holder. For centrally authorised products which are likely to require major risk minimisation activities, marketing authorisation holders are encouraged to discuss the feasibility of how they might be implemented with individual national competent authorities during the building of the risk minimisation plan.

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 are complied with prior to the launch of the product in a particular territory.

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.

V.C.8. Transparency

The Agency and Member States shall make publically available public assessment reports and summaries of risk management plans [REG Art 26(1), DIR Art 106].

For centrally authorised products the Agency will:

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

To promote public health, the Agency will make available (either on request or via its web portal):

- any questionnaires included in RMPs for centrally authorised products which are used to collect information on specified adverse reactions;
- details, which may include copies, of educational material or other additional risk minimisation activities required as a condition of the marketing authorisation;
- details of disease or substance registries requested as part of the pharmacovigilance plan for centrally authorised products.

The national competent authorities will provide details of how they intend to implement Article 106 of Directive 2001/83/EC.