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3 Guideline on good pharmacovigilance practices (GVP)

4 Module V – Risk management systems

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

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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 small numbers of subjects in clinical trials, 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, affect 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 efficacy 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 will be tailored to regional specifics. 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 a different RMP for each region although there will be several elements which are common to all. 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 website[1].

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:

- an adverse reaction which was seen in non-clinical safety studies which has not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of, 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.

[1] www.ema.europa.eu

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.

Important identified risk, important potential risk or important missing information

An identified risk, potential risk or missing information that could have a significant impact on the risk-benefit balance of the product and/or have implications for public health.

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.

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.

Target population (treatment)

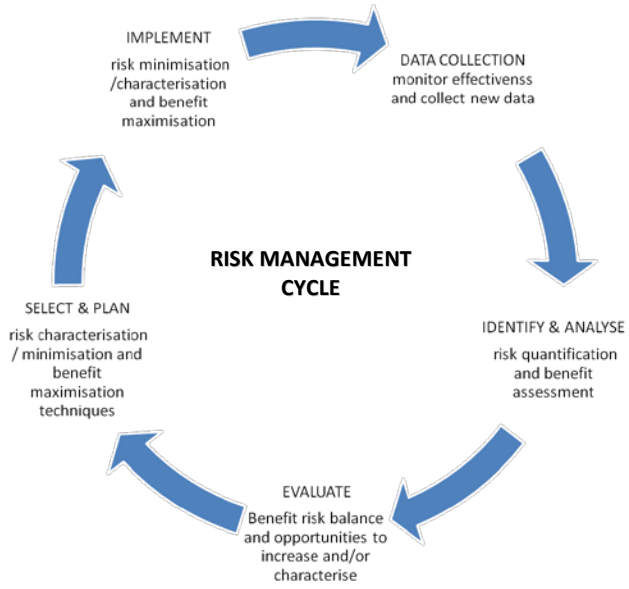
The patients who might be treated by the medicinal product according to the indication(s) and contraindications in the authorised product information.

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 (particularly 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 (see Annex IV). Outside of the EU, some territories may have local legislation enshrining either risk management in general or adopting the specific ICH guidance or have developed local guidance. For healthcare professionals, product information, medical treatment guidelines and any materials produced by marketing authorisation holder, competent 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, patients who understand the potential risks and benefits 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 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 did 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..

Producing a RMP requires the input of different specialists and departments within a applicant/marketing authorisation holder. 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 study planned to address them. The design of risk minimisation activities should involve communication experts and, where appropriate, patients and/or healthcare professionals. Since a benefit 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.

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;
- ensure the implementation of risk minimisation activities at a national level;
- effectively communicating to stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, healthcare physicians, patient groups, learned societies etc;

- ensuring marketing authorisation holders of generic and/or similar biological medicinal products make similar changes when changes are made to the reference medicinal product risk minimisation measures;
- 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 a reference medicinal product.

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

The content of RMP must:

- 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 [IM Annex II.1].

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 in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase;
- plan 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 [IM Annex II.2] 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 means that the RMP can easily be updated. 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 two ways: by reducing the number of modules which need to be submitted for products meeting certain conditions, and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the risks and uncertainties of the product.

An overview of the parts and modules of the RMP is provided below [IM Annex II.2]:

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

Part I Product(s) Overview

Part II Safety Specification

- **Module SI: Epidemiology of the indication(s) and target population(s)**
- **Module SII: Non-clinical part of the Safety Specification**
- **Module SIII: Clinical trial exposure**
- **Module SIV: Populations not studied in clinical trials**
- **Module SV: Post-Authorisation Experience**
- **Module SVI: Additional EU requirements for the Safety Specification**
- **Module SVII: Identified and potential risks**
- **Module SVIII: Summary of the safety concerns**

Part III Pharmacovigilance Plan

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 RMP

Part VII Annexes

Where an RMP concerns different medicinal products, a separate RMP part VI must be provided for each medicinal product [IM Annex II.2].

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. Copies of literature referenced in the RMP should be included in RMP annex 11.

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 1394/2007[2], 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.

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:

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

- 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);
  - proposed (if applicable);
- dosage:
  - current (if applicable);
  - proposed (if applicable);
- pharmaceutical forms and strengths:
  - current (if applicable);
  - proposed (if applicable);
- whether the product is the subject of additional monitoring in the EU; and
- worldwide regulatory status by country (including EEA) (date approval/refusal, date marketed, current licence status, explanatory comments).

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
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, including quality aspects if relevant in relation to safety and efficacy of the product profile, and whether the disposal of the product which 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. This population is also at increased 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.

The marketing authorisation holder 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. A very short review of where the medicinal product fits in the normal therapeutic armamentarium should be provided.

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, and the relevance of the findings to the use in humans, should be discussed. Also quality aspects if relevant in relation to safety (e.g. important information on the active substance or its impurities, e.g. genotoxic impurities) should be discussed. If the 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. 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 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.

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) 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.

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 so the cumulative effect of multiple impairments and multiple medications should be evaluated. Consideration of whether particular laboratory screening should be done routinely before use 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. If contraception was a condition of trial entry, the discussion on pregnancy should also include an analysis of the reasons why the measures put in place failed (if relevant), 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

  The experience of use in patients with different racial and/or ethnic origins should be discussed and the implications on efficacy, safety or pharmacokinetics in the target population. If it is likely that efficacy may be affected by race or ethnicity, consideration as to whether post-authorisation efficacy studies are necessary with a cross reference to RMP part IV if appropriate.

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, including use in the special populations mentioned in RMP module SIV, the number of patients included in observational studies where safety data has been collected and any regulatory action taken to update information on the safety of the medicinal product**.**

V.B.8.5.1. RMP module SV section "Regulatory and marketing authorisation holder action for safety reasons"

List any regulatory action in any market (including those initiated by the marketing authorisation holder) taken in relation to a safety concern. This list should be cumulative, and specify the country, action taken and the date. For updates to the RMP only, actions taken since the last submission of the RMP should be described with a brief description of the reasons leading to the action. 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 taken 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.

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

Where post-authorisation use has occurred 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.8.6.5.). 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 SVI 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 "Indicated use versus actual use"

For updates to the safety specification, specific reference should be made as to how the actual pattern of exposure has differed from that predicted in RMP module SVII, and from the indication(s) and contraindications in the summary of product characteristics (off-label use). Information from drug utilisation studies (or other observational studies where indication is included) should be included here including drug utilisation studies which have been requested by national competent authorities for purposes other than risk management.

Off-label use, includes, amongst others, use in non-authorised paediatric age categories, and use in other (non EU-authorised) indications outside of the clinical trial setting.

When there has been a concern 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.

Use in clinical trials conducted as part of the marketing authorisation holder's development programme should be included only in RMP module SII and not in this RMP module SV section.

V.B.8.5.5. RMP module SV section "Epidemiological study exposure"

Marketing authorisation holders should provide a listing of epidemiological studies which have included/include the collection of safety data. This listing should include studies which the marketing authorisation holder has undertaken itself or funded by a grant, whether specific or unconditional. 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 ongoing). If the study has been published, a reference should be included in this RMP section and the publication provided in RMP annex 8.

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

Some safety issues 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 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 SVa 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. 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"

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 the 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 Procedure[3]), 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 Use[4] 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 and where appropriate, medication error should be included as a safety concern.

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, medication error should be included as a safety concern and the measures 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 "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 SVI or SVIa. 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

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

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 SVI and SVIa.

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.8.6.6. RMP module SV section "Projected post-authorisation use"

For pre-authorisation RMPs, or when applying for a significant change to the indication, the MAH should provide details on the projected pattern of use, estimated population drug usage over time, place in therapeutic armamentarium and market position in the EU.

Potential for off-label use

The potential for off-label use should be discussed. 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.

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.8.7. 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 include the identified and potential adverse events/reactions, identified and potential interactions with other medicinal products, foods and other substances, and the pharmacological class effects. To avoid repetition, products classified as advanced medicinal products should omit this module and provide information in RMP module SVIIa.

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

Safety concerns 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 "Details of important identified and potential risks"

This RMP section should provide more information on the most 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. Normally, any risk 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. Interactions which are of significant clinical importance and important pharmacological class effects should also be included. 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, avoidability or possibility of detection at an early stage);
- 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 inclusion could cause confusion. For example, if one product were a depot formulation and another product an oral formulation, there would be risks associated with the injection which would not be applicable to the oral form. Risks specific to a paediatric medicinal product, e.g. sexual maturation and growth, will not be applicable to an adult only product.

V.B.8.7.3. 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 in the RMP section on identified and potential risks (see V.B.8.7.2.).

V.B.8.7.4. RMP module SVII section "Pharmacological class effects"

Important risks believed to be common to the pharmacological class should be discussed here. For risks included in the RMP section on important and identified and potential risks 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 pharmacological class.

If a risk which is common to other members of the pharmacological class is not thought to be a safety concern with the medicinal product, and hence is not included as an identified or potential risk, the evidence supporting this should be provided.

V.B.8.8. RMP module SVII "Identified and potential risks (ATMP)"

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.8.8.2. 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"

Safety concerns 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.8.8.2. RMP module SVII section "Details of important identified and potential risks"

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/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:

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

- 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);
  - transmammary 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.

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 (safety) 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). 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.

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 6 and will be made publically 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 (safety) activities"

Applicants/marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may not have any safety data on use longer than three years 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 assess the effectiveness of risk minimisation activities. The applicant/marketing authorisation holder should include all studies designed to address the safety concern and those which might provide useful safety information even though the particular safety concern might not have been the primary focus. 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 to investigate a specific safety concern should also be included. If, when reviewing a study protocol, a study is thought to be primarily promotional, 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 Pharmacoepidemiology[7]. For studies involving children, the Guideline on Conduct of Pharmacovigilance

[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

for Medicines Used by the Paediatric Population[8] 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.

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 5.

Synopses of study reports from additional pharmacovigilance activities should be included in RMP annex 8. 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 plan updated accordingly.

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

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.

a. 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 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.

b. 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

[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

timescale laid down by 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.

c. Registries

Registries are prospective non-interventional cohort studies and as such should follow the appropriate standards and scientific guidelines. 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, as part of an agreed RMP, the applicant/marketing authorisation holder institutes a registry, 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 should apply to similar biological products.

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

If there are additional pharmacovigilance activities, the action plan for each safety concern should be presented according to the following structure:

- safety concern;
- objective of proposed action(s);
- action(s) proposed;
- milestones for evaluation and reporting.

One of the actions proposed for each safety concern will nearly always be "routine pharmacovigilance." As well as listing any additional activities under "Action(s) proposed," protocols (draft or otherwise) for any formal studies should be provided in RMP annex 5. This will enable the feasibility of the study and its ability to provide answers to be assessed. It is recommended that the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[9] including the Checklist of Methodological Standards for ENCePP Study Protocols[10], should be referred to when considering epidemiological protocol design.

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

A summary table of all additional pharmacovigilance activities should be provided including the expected dates of milestones.

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

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

[9] ENCePP Guide on Methodological Standards in Pharmacoepidemiology" EMA/95098/2010; available on http://www.encepp.eu
[10] Checklist of Methodological Standards for ENCePP Study Protocols", EMEA/540136/2009; available on http://www.encepp.eu
[11] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

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 include a paediatric indication in 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 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.

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

Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should 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.

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

As explanation for any efficacy studies proposed and to provide background that can be used in the RMP summary, there should be a summary of the efficacy of the product and what studies and endpoints it was based upon. The robustness of the endpoints on which the efficacy evaluation is based should be briefly discussed. This should be brief (one page maximum).

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

- 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.

Where the RMP covers more than one medicinal product, the above information should be provided by medicinal product to permit easy extraction for the summary module.

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 7.

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

On the basis of the safety specification, the applicant/marketing authorisation holder should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should

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

provide details of the risk minimisation activities which will be taken to reduce the risks associated with individual safety concerns. It is difficult 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 activity.

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:

- a substance where there are products with both prescription only and non prescription legal status;
- substances 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 specialised knowledge will be distinct. For example a substance which causes important QT prolongation would most likely not need educational material if the product is intended for use by cardiologists but might need it if intended for use in general practice or orthopaedic surgery;
- substances where there are major risks which differ according to the target population.

Risk minimisation activities may consist of routine risk minimisation (e.g. recommendations in the locally authorised product literature) or additional risk minimisation activities (e.g. Dear Healthcare Professional Communication/educational materials/controlled distribution systems). All risk minimisation activities should have a clearly identifiable objective. Risk minimisation measures and the assessment of their effectiveness 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 happen with 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

Limiting the number of units prescribed is another routine risk management activity. This can be useful if regular testing or review is needed. By limiting the number of units, the patient will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the

[13] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

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

Controlling the conditions under which a medicinal product may be made available could reduce the risks associated with its use or misuse. This might 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. This is commonly referred to as the "legal status" of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medicinal prescription. It may also restrict where the medicinal product can be administered (e.g. to a hospital) or by whom it may be prescribed (e.g. specialist).

For medicinal products only available upon 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. When considering classification 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.

However, the definition of what constitutes a specialist is not uniform throughout the Member States so in practice the provisions of the last indent are 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 restriction 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 may be specified rather than a location: e.g. "use in a setting where resuscitation equipment is available."

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 he 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)].

There is 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 routine risk minimisation activities. Additional risk minimisation activities should only be suggested when necessary for the safe and effective use of the medicinal product. Many additional risk minimisation tools are based on communication which goes beyond the summary of product characteristics (SmPC) and the package leaflet. Further consideration of additional risk minimisation activities is provided in Module XVI.

If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided. Only activities related to safe and effective use should be included and these should be science based, and developed and provided by suitably qualified people.

It is essential that appropriate specialised experts are consulted at all stages and applicants/marketing authorisation holders are also encouraged to discuss risk minimisation plans with the competent authorities early on. 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.

For centrally authorised products, only activities agreed by the CHMP will be allowed in the risk minimisation plan and any other activities which the CHMP considers 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 detailed in annex II and annex 127a of the CHMP Opinion as appropriate. Where appropriate, full details of additional risk minimisation activities (including draft educational material) should be provided in RMP annex 9.

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 it is piloted before the final version is agreed.

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 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 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 obligation may also be required for other patient material e.g. patient alert cards and patient monitoring cards.

Further guidance on individual risk minimisation activities 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:

- safety concern;
- objective of proposed action(s);
- routine risk minimisation activities;
- additional risk minimisation activities (if any), individual objectives and justification of why needed;
- how the effectiveness of the 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) should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

V.B.11.4. Updates of the risk minimisation plan

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.

In general, the focus should be on information which has emerged during the reporting period or since implementation of the most recent risk minimisation activity(ies). Such information may be presented by region, if applicable/relevant. Results of formal assessment(s) of risk minimisation activities should always be included. 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. The marketing authorisation holder should also comment on whether additional or different risk minimisation activities are needed for each safety concern.

V.B.11.5. 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.

If a particular risk minimisation strategy proves ineffective then alternative activities need to be put in place. 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.

General guidance on monitoring the effectiveness of risk minimisation activities is included in Module XVI.

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)]. 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 lack of knowledge [IM Annex II.2]. This summary should be written for the lay reader and, to present a balanced picture, the risks discussed in the RMP should be put into context with the benefits of the medicinal product.

In addition, summary tables of the RMP showing the safety concerns, risk minimisation activities and plans for post-authorisation efficacy and pharmacovigilance development will be included in the European Public Assessment Report (EPAR).

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

- overview of disease epidemiology;
- summary of benefits/efficacy (see V.B.10.1.);
- summary of safety concerns (in lay language);
- tables:
  - summary of risk minimisation activities by safety concern;
  - planned post-authorisation development plan (safety and efficacy) including specific details (and explanation) of any activities which are conditions of the marketing authorisation.

Further details and a template for this section will be developed.

V.B.12.1. RMP part VI section “Overview of disease epidemiology and summary of expected benefits”

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 in the epidemiology of the disease. 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.

The summary from RMP part IV section “Presentation of efficacy data” (see V.B.10.1.) should be used for the expected benefits/efficacy.

V.B.12.2. RMP part VI section “Summary of safety concerns (in lay language)”

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. For important potential risks the reasons why the risk may occur (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”. For important missing information it should be stated that it hasn’t been studied, the relevance to the target population and what the recommendations are, e.g. contraindication, use with caution.

V.B.12.3. RMP part VI section “Summary table of risk minimisation activities by safety concern”

This should list the safety concerns and provide a summary of the risk minimisation activities proposed for each concern. 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 table with the headings suggested in module SVI or SVIa. If there is more than one risk minimisation plan (RMP part V) then separate tables for each plan should be provided.

When detailing the risk minimisation activities in relation to the summary of product characteristics (SmPC), the actual text of SmPC sections 4.3 and 4.4 (if relevant) should be used. However if the SmPC sections are very long, a précis should be provided. For risk minimisation activities involving other parts of the SmPC a summary of what is in each SmPC section should be provided. For SmPC section 4.8, indicating “labelled in section 4.8” is sufficient. The corresponding information in the package leaflet should also be provided.

V.B.12.4. RMP part VI section “Planned post-authorisation efficacy and pharmacovigilance development”

This table should provide a list of the planned activities in terms of efficacy studies and further investigation of safety concerns. The purpose is to provide an overview of the planned post-authorisation development of the product in relation to efficacy and pharmacovigilance and the milestones associated with each study or activity. This table would combine the tables from sections V.B.9.4. and V.B.10.1.. Each row of the table should include the reason for the study, the name of the study, brief details, timelines and milestones.

V.B.12.5. RMP part VI section "Summary of changes to risk management plan by time"

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date new safety concerns were added or existing ones removed, dates 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 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 following annexes:

RMP annex 1: Interface between RMP and Eudravigilance/EPITT (electronic only) (see {reference})

RMP annex 2: Current (or proposed if product is not authorised) summary of product characteristics (SmPC) and package leaflet

RMP annex 3: Synopsis of ongoing and completed clinical trial programme

RMP annex 4: Synopsis of ongoing and completed pharmacoepidemiological study programme

RMP annex 5: Protocols for proposed and ongoing studies in RMP part III

RMP annex 6: Specific adverse event follow-up forms

RMP annex 7: Protocols for proposed and ongoing studies in RMP part IV

RMP annex 8: Newly available study reports

RMP annex 9: Details of proposed additional risk minimisation activities (if applicable)

RMP annex 10: Example(s) of actual 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 (in English only or as requested by the national competent authority)

RMP annex 11: 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 submitted is 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 and 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.1. Common sections between RMP and PSUR

RMP section	PSUR section
Sub-section of part I – "Product overview"	Section 2 – "Worldwide marketing approval status" and EU marketing approval status included in the EU Regional Appendix
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 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 II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterisation of risks"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"

V.B.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 haven't 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?
- 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 (as provided in the description of the pharmacovigilance system) 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?
- Does the RMP include appropriate proposals to monitor medication errors?
- 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?
- Are any proposed studies promotional (i.e. a study which does not have a valid scientific question as its primary aim and is designed to increase use of the product)?
- How robust is the efficacy data and do further efficacy studies need to be requested as a condition of the marketing authorisation?

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. 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 the existing risk minimisation measures been successful?
- 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 qualified person responsible for pharmacovigilance in the EU (QPPV). 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

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 [IM Annex II.1] 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.

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.

Applications for innovative products where an 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;
- 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.

For situations where there is no mandatory legal requirement for the submission of an RMP (e.g. significant change to a marketing authorisation), the need for it should be discussed with the Agency or national competent authority, as appropriate, well in advance of the submission. At the submission of the application in these circumstances, either an RMP, or a justification of why the applicant believes

an RMP is not needed, should be included in section 1.8.2 of the marketing authorisation application dossier.

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 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 submission 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 SII – SV may be omitted. RMP module SVI 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 and the section on planned post-authorisation development in RMP part VI may be omitted.

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.

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 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.

Table V.2. 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 SVIa	Part II, Module SVII	Part II, Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent [1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓						✓	✓	✓	✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	Λ	Λ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	Λ	Λ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Well established use ”	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
“Same active substance”	✓	✓	*	*		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Application under Article 10(c) of Directive 2001/83 as amended

[2] Application under Article 58 of Regulation 726/2004 as amended

Λ 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 [IM Annex II.3]. 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 be included as a condition of the marketing authorisation. 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.

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

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 ongoing CHMP discussions, e.g. changed indications, changes in SmPC wording which affect risk minimisation. The last version submitted before the Opinion, shall be considered the "current version" whether or not a formal assessment report of the RMP is provided to the applicant/marketing authorisation holder.

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 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 to ensure that the conditions and/or restrictions are implemented by the marketing authorisation holder in their territory. How these conditions 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 Member States will provide details of how they intend to implement Article 106 of Directive 2001/83/EC.