

# **Guideline on Good Pharmacovigilance Practices**

Module VI – Risk  
Management Systems

TURKISH MEDICINES AND MEDICAL  
DEVICE AGENCY

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## **SECTION I**

### **Introduction**

#### **1.1. Introduction**

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials, 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 risk-benefit balance is judged to be positive for the target population. 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.

In assessing the risk-benefit balance at the time of authorisation, the assumption is made that these benefits and risks apply to the whole target population. However, there may be subsets of patients for whom the risk is greater than that for the target population as a whole, or in whom the benefit may not be as great. In addition, efficacy in the clinical trial setting may not reflect the true effectiveness of the medicinal product in everyday medical practice and so the risk-benefit balance of a medicinal product as assessed at the time of authorisation will inevitably change post-authorisation. Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimisation activities will need to be tailored to the system in place in a particular country or global region. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a medicinal product may also vary between regions. Therefore a product may have different versions of a RMP for each region although there will be core elements which are common to all. For example much of the safety specification will be the same regardless of where the medicinal product is being used but the epidemiology of the disease may vary between e.g. Africa and Europe, and there may be additional or fewer safety concerns depending upon the target population and indication.

Risk management, is applicable to medicinal products at any point in their lifecycle. 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.

## **SECTION II**

### **Structures and processes**

#### **2.1. Terminology**

##### 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.

Adverse reactions stated in section 4.8 of Summary of Product Characteristics are accepted as identified risk. However, the reactions that are related to the class which is not identified specifically, even though the reactions are mentioned in the SPC, are excluded (these are accepted as potential risk).

##### Potential risk

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

Examples include:

- Toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group, on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship;
- A signal arising from a spontaneous adverse reaction reporting system;
- An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

##### Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

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

##### Important identified risk and important potential risk

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

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

#### Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [Safety of Medicinal Product Directive Art 4(1)ö].

#### Risk management plan

A detailed description of the risk management system [Safety of Medicinal Product Directive Art 4(1)ö].

For this purpose; the RMP has to determine and identify the safety profile of the specified medicinal product(s); has to provide guidance for the preparation of a more detailed safety profile for the specified medicinal product(s); has to document necessary measures to prevent or limit the risks that are related to the medicinal products, as well as to provide within this context an assessment regarding the effectiveness of the interventions in question; and has to certify the activities, if any, carried on to fulfill the liabilities requested post authorisation by the Competent Authority.

#### Risk minimization activity (used synonymously with risk minimization measure)

An 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.

These activities can be from the routine risk minimization activities (i.e. productcharacteristic) or additional risk minimization activities (i.e. communication with the health care providers or patients/training materials).

#### Safety concern, Safety doubt

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

#### Target population (treatment), Target treatment population

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

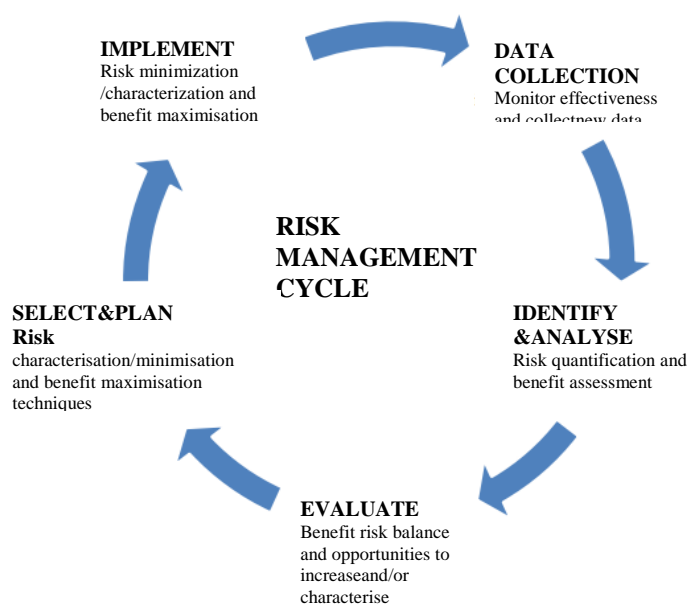
## **2.2. Principles of risk management**

The overall aim of risk management is to ensure that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

This can be done either by increasing the benefits or by reducing the risks. Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (including those linked to the Safety Specification section on Missing Information) and their integration, where necessary, in the RMP may enable resources to be used more efficiently and for risks to be put into context. The RMP therefore includes the planning of such studies

The principles of risk management are the same regardless of stakeholder or territory (see Figure1).

**Figure 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.

### **2.3. Responsibilities for risk management within an organization**

Within in our country, the principle organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the competent authorities who regulate them is Turkish Medicines and Medical Devices Agency.

#### **2.3.1. Marketing authorisation holders and applicants**

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

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

For risk management primary document and process with in compliance with legislation should conform the principals at "The International Conference on Harmonisation of Pharmacovigilance Planning (ICH) Guideline E2E".

ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation. However it was acknowledged at the time of development of ICH E2E that risk minimisation was an integral part of risk



management planning. Details of how the safety specification and pharmacovigilance plan are integrated within the RMP and the detailed structure and format are provided in 2.5 to 2.7. Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a RMP is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorization applicant/holder who should ensure oversight by someone with the appropriate scientific background within the company.

## **2.4. Objectives of a risk management plan**

RMP must contain the following elements which:

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

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

- describe what is known and not known about the safety profile of the concerned medicinal product(s);
- indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);
- include a description of how the effectiveness of risk minimisation measures will be assessed.

The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. For products requiring periodic safety update reports (PSURs), certain (parts of) modules may be used for both purposes (see 2.14.).

## **2.5. Structure of the risk management plan**

The RMP consists of seven parts. Certain parts of the RMP, in particular the safety specification, are subdivided into modules [IR Annex 1] so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan.

Differences between indications, formulations and target populations, if several medicinal products have the same active substance, will be similarly accommodated by dividing the relevant parts of the RMP into modules and/or sections. The modular structure also means that the RMP can be updated easily. As the product matures, some RMP modules or sections may cease changing – for example non clinical studies may stop at a certain time as may clinical trials. These RMP modules can be effectively “locked” until new data needs to be added. In addition, certain RMP modules may be omitted in specific circumstances (see 3.3.1.). An overview of the parts and modules of the RMP is provided below:

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

<b>Part I</b> Product(s) overview
<b>Part II</b> Safety specification
<b>Module I</b> Epidemiology of the indication(s) and target population(s)
<b>Module II</b> Non-clinical part of the safety specification
<b>Module III</b> Clinical trial exposure
<b>Module IV</b> Populations not studied in clinical trials
<b>Module V</b> Post-authorisation experience
<b>Module VI</b> Additional requirements of other health authorities for the safety specification
<b>Module VII</b> Identified and potential risks
<b>Module VIII</b> Summary of the safety concerns
<b>Part III</b> Pharmacovigilance plan
<b>Part IV</b> Plans for post-authorisation efficacy studies
<b>Part V</b> Risk minimisation measures (including evaluation of the effectiveness of risk minimization measures)
<b>Part VI</b> Summary of the risk management plan
<b>Part VII</b> A

Where a RMP concerns more than one medicinal product, a separate RMP part VI must be provided for each medicinal product.

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.

To aid consistency between the information provided in the common technical document (CTD) and the RMP, the table below indicates the location of information in the CTD is summarised for the RMP:

**Table 1 Mapping between RMP modules and CTD**

<b>RMP</b>	<b>CTD</b>
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality
Module I Epidemiology of the target population	Module 2.5 Clinical overview
Module II Non-clinical part of safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module III Clinical trial exposure	Module 2.7 Clinical summary Module 5 Clinical Study reports

Module IV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module V Post authorisation experience	Module 2.5 Clinical overview
Module VII Identified and potential risks	Module 2.5 Clinical overview (including benefit risk conclusion) Module 2.7 Clinical summary (SPC)
Module VIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post authorisation efficacy studies	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

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

## 2.6. Detailed description of each part of the risk management plan

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

Under Regulation (EC) No 1394/20072, certain products for human medicinal use are categorized within the EU as advanced therapy medicinal products (ATMPs). These products are fully defined in the above Regulation but broadly comprise gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products. Because of the nature of these products, risks may occur which are not normally a consideration with other medicinal products including risks to living donors, risks of germ line transformation and transmission of vectors. For this reason, for ATMPs, RMP module VII Identified and potential risks (ATMP) should replace RMP module VII Identified and potential risks as this provides greater flexibility in consideration of the additional risks.

## 2.7. RMP part I “Product overview”

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

This part 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:

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

### **2.8. 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). This part should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information. Missing information is defined as: gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

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 balance 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 I-V, VII and VIII correspond to safety specification headings in ICH-E2E. RMP module VI includes additional elements required to be submitted to other health authorities.

**Module I** Epidemiology of the indication(s) and target population(s)

**Module II** Non-clinical part of the safety specification

**Module III** Clinical trial exposure

**Module IV** Populations not studied in clinical trials

**Module V** Post-authorisation experience

**Module VI** Additional requirements of other health authorities for the safety specification

**Module VII** Identified and potential risks

**Module VIII** Summary of the safety concerns

RMP modules III–V form the “Limitations of the human safety database” part of the ICH-E2E safety specification and these, with the addition of RMP modules I and VII form the clinical part of the safety specification. RMP modules VI and the ATMP version of VII are EU and our country specific although the topics may apply in any territory.

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

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

### **2.8.1. RMP module I “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 Turkey of the proposed indication.

Information should be provided on the important co-morbidities in the target population. For example: if a medicinal product is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not taking the medicinal product. Estimation of the risk in the target population, as compared with the same age/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

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

### **2.8.2. RMP module II “Non-clinical part of the safety specification”**

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

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

- other toxicity-related information or data.

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

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

### **2.8.3. RMP module III “Clinical trial exposure”**

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:

- age and gender;
- indication;
- dose;
- racial origin (see also 2.8.4.).

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

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

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

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

For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

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

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

#### **2.8.4. RMP module IV “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 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 number of patients studied, cumulative exposure (e.g. specific organ toxicity), 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 VIII.

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

- Paediatric population  
Children (from birth to 18 years with consideration given to the different age categories as per ICH-E11, or, if justified, to other developmentally meaningful groups i.e. taking into account specific organ maturation). If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.
- Elderly population  
Implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum. The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The cumulative effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory

screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular any adverse reactions which might be of special concern in the elderly e.g. dizziness or central nervous system effects should be explored.

- Pregnant or breast-feeding women

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

- Patients with hepatic impairment

- Patients with renal impairment

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

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

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

- Sub-populations carrying known and relevant genetic polymorphism

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

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

- Patients of different racial and/or ethnic origins

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

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



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

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

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

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

#### **2.8.5. RMP module SV “Post-authorisation experience”**

The purpose of this RMP module is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP module IV. It should also include brief information on the number of patients included in completed observational studies conducted either to elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicinal product should also be provided in this module.

##### ***2.8.5.1. RMP module SV section “Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons”***

List any significant regulatory action (including those initiated by the marketing authorisation holder), in any market, taken in relation to a safety concern. Significant regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation.

This list should be cumulative, and specify the country, action taken and the date as appropriate. Rollout in multiple countries of a new safety statement initiated by the MAH can be presented as one action.

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

##### ***2.8.5.2. RMP module V section “Non-study post-authorisation exposure”***

Where marketing of the medicinal product has occurred, the applicant/marketing authorisation holders 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. Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment.

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

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

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

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

#### ***2.8.5.3. RMP module V section “Post-authorisation use in populations not studied in clinical trials”***

Where there are data on post-authorisation use in the special populations identified in RMP module IV 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 VI (see 2.8.6.6.). Information on the safety profile of the medicinal product in these special populations, as compared with the rest of the target population, should also be provided. In particular, any information regarding an increased or decreased benefit in a special population should be provided. Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP module VII but reference should be made in this section as to which risks and populations are affected.

#### ***2.8.5.4. RMP module V section “Post-authorisation off-label use”***

Post marketing, updates to the safety specification, should include information on off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the authorised product information for a medicinal product. Off-label use includes use in non-authorised paediatric age categories.

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

#### ***2.8.5.5. RMP module V section “Epidemiological study exposure”***

Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by

the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

#### **2.8.6. RMP module VI “RMP module VI “Additional requirements regarding other health authorities for the safety specification”**

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

##### ***2.8.6.1. RMP module VI section “Potential for harm from overdose”***

Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP module VIII and appropriate risk minimisation proposed in RMP part V.

##### ***2.8.6.2. RMP module VI 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 VII (ATMP) may be made.

##### ***2.8.6.3. RMP module VI section “Potential for misuse for illegal purposes”***

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

##### ***2.8.6.4. RMP module VI section “Potential for medication errors”***

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

1. wrong medication;

2. wrong dose (including strength, form, concentration, amount);
3. wrong route of administration;
4. wrong patient

Applicants/marketing authorisation holders should consider routinely the likelihood of medication errors. In particular, they should assess, prior to marketing, common sources of medication errors. During the development phase and during the design of a medicinal product for marketing, the applicant needs to take into account potential reasons for medication error. The naming (taking into account the 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.

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

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

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

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

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

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

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

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

#### ***2.8.6.5. RMP module VI section “Potential for off-label use”***

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

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 other countries discussed.

#### **2.8.6.6. RMP module VI section “Specific paediatric issues”**

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

##### 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 VII. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.

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

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

Cross-reference may be made to RMP modules IV and VII and VII.

##### 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 V section “(Nonstudy) post-authorisation exposure” (see 2.8.5.2.) and in RMP module V section “Post-authorisation use in populations not studied in clinical trials” (see 2.8.5.3.).

#### **2.8.7. RMP module VII “Identified and potential risks”**

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

*Because of the need for different additional categories of risks to be considered with advanced*

*therapy medicinal products, a different version of RMP module VII is available for products classified as advanced medicinal products. Only one version (either sections 2.8.7.1 - 2.8.7.5 or sections 2.8.8.1 – V.B.8.8.3) of RMP module VII should be provided in a RMP.*

#### ***2.8.7.1. RMP module VII section “Newly identified safety concerns”***

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

#### ***2.8.7.2. RMP module VII section “Recent study reports with implications for safety concerns”***

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

#### ***2.8.7.3. RMP module VII section “Details of important identified and potential risks from clinical development and post-authorisation experience”***

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

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also 2.1). Normally, any risk which is clinically important and which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person’s life, and which could lead to serious consequences if untreated should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

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

#### **Presentation of risk data:**

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

- frequency;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life);
- risk factors (including patient factors, dose, at risk period, additive or synergistic

factors);

- preventability (i.e. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

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

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

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

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

For 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 intravenous 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 (with different administration routes and different indications), it may be appropriate to categorise the risks to make it clearer which risks relate to which product. Headings which could be considered include:

- Risks relating to the active substance

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

- Risks related to a specific formulation or route of administration

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

- Risks relating to a specific target population

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

- Risks associated with switch to non-prescription status.

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

#### ***2.8.7.4. RMP module VII section “Identified and potential interactions including fooddrug and drug-drug interactions”***

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

#### ***2.8.7.5. RMP module VII section “Pharmacological class effects”***

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

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

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

#### **2.8.8. RMP module VII “Identified and potential risks (ATMP version)”**

Advanced therapy medicinal products (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products (see Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products).

For this reason, for ATMPs, this ATMP specific version of RMP module replaces the standard



RMP module VII.

Although not all of the risks listed in section 2.8.8.3 are unique to ATMPs or applicable to all ATMPs, they represent the most relevant ones which need to be considered.

#### ***2.8.8.1. RMP module VII section “Newly identified safety concerns (ATMP)”***

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

#### ***2.8.8.2. RMP module VII section “Recent study reports with implications for safety concerns (ATMP)”***

Study reports (either interim or final), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (e.g. RMP module II; section 2.8.8.3; RMP Module VI and RMP Module VII).

#### ***2.8.8.3. RMP module VII section “Details of important identified and potential risks(ATMP)”***

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

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

- risks to living donors, for instance:
  - risks to living donors related to their conditioning prior to procurement (e.g. immunosuppression, cytotoxic agents, growth factors);
  - risks to living donors related to surgical/medical procedures used during or following procurement, irrespective of whether the tissue was collected or not;
  
- risks to patients related to quality characteristics of the product, in particular:
  - species of origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing, and the safety testing performed;
  - characteristics of vectors for gene therapy medicinal products;
  - biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
  - quality assurance and characteristics of the finished product in terms of defined composition, stability, biological activity, and purity with reference to non-physiologic proteins and fragments thereof;
  - risk related to transmissible diseases (e.g. viral, bacterial, parasitical infections and

infestations, but also malignant disease);

- risks to patients related to the storage and distribution of the product, for instance:
  - risks related to preservation, freezing and thawing;
  - risks of breaking the cold chain or other type of controlled temperature conditions;
  - risks related to stability of the product;
  
- risks to patients related to administration procedures, for instance:
  - biologically active substances used in preparation of the product prior to administration (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
  - risks related to conditioning of the patient;
  - risks of related medical or surgical procedures (e.g. anaesthesia, infusion, transfusion, implantation, transplantation or other application method);
  - risks related to clinical follow-up (e.g. immunosuppression as co-medication or as necessary for treatment of complications, diagnostic procedures, hospitalisation);
  - risks related to mistakes or violations of the standard procedures for administration of the product (e.g. different administration procedures used by different healthcare establishments/healthcare professionals resulting in differing results);
  
- risks related to interaction of the product and the patient, for instance:
  - unwanted immunogenicity and its consequences (including e.g. anaphylaxis, graft versus host disease, graft rejection, hypersensitivity reactions, immune deficiencies);
  - risks related to both intended and unintended genetic modification of the patient's cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy);
  - early and late consequences of homing, grafting, differentiation, migration and proliferation;
  - risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene, altered expression of the host's genes);
  
- risks related to scaffolds, matrices and biomaterials (e.g. biodegradation, mechanical factors);
  
- risks related to persistence of the product in the patient, e.g.:
  - availability of rescue procedures or antidotes and their risks;
  - late complications, particularly malignancies and auto-immunity;
  - considerations on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the respective disease on the product, or vice versa impact of the product on those other therapies (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction);
  
- risks related to re-administration, for instance:
  - immune reactions - anaphylaxis, neutralising antibodies;
  - risks related to repeated surgical or administration procedures;

- risks to close contacts, for instance:
  - based on the environmental risk assessment, virus shedding and its consequences;
- specific parent-child risks, for instance:
  - risk of germ line integration of transgene, or other genetic transformation of the germ line;
  - foetal transmission (of e.g. vectors, biologically active substances, cells, infectious agents);
  - trans-mammary exposure of children in breast-feeding women (to e.g. vectors, biologically active substances, cells, infectious agents).

### **2.8.9.RMP module VIII “Summary of the safety concerns”**

At the end of the RMP part “Safety specification” a summary should be provided of the safety concerns.

A safety concern is:

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

It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information. The ICH-E2E Guideline uses the terms safety issue and safety concern interchangeably with the same definition for safety concern.

The change of the EU term, to name this concept “missing information” rather than “important missing information”, is to be clear that in the EU a marketing authorisation cannot be granted if there are unacceptable gaps in knowledge a marketing authorisation shall be refused if the quality, safety or efficacy are not properly or sufficiently demonstrated. Due to the same reason the consideration of “missing information” rather than “important missing information” is adopted in our country.

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 VII, 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.

### **2.9. RMP Part III “Pharmacovigilance plan”**

The purpose of the pharmacovigilance plan is to discuss how the applicant/marketing authorization 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 missing information will be sought.

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

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module VIII 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.

### **2.9.1. RYP RMP part III section “Routine pharmacovigilance activities”**

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for pharmacovigilance contained within “Regulation on Safety of Medicines”. 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.

Competent authority 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 IV). If these recommendations include recording of tests (including in a structured format) which would form part of normal clinical practice for a patient experiencing the adverse reaction then this requirement would still be considered as routine. The routine pharmacovigilance section of the pharmacovigilance plan should be used in these circumstances to explain how the applicant will modify its routine pharmacovigilance activities to fulfil any special competent authority recommendations on routine pharmacovigilance.

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

#### Specific adverse reaction follow-up questionnaires

Başvuru/ruhsat sahibinden talep edildiği veya başvuru/ruhsat sahibinin kullanmayı Where an applicant/marketing authorisation holder is requested, or plans to use, specific questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. Applicants/marketing authorisation holders are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.

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

### **2.9.2. RMP part III “Additional pharmacovigilance activities” subsection**

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

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

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

Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The applicant/marketing authorisation holder should include all studies designed to address the safety concern or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders, voluntarily, or pursuant to obligations imposed by a competent authority. 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 not to have as its primary focus one of the objectives of a Post Authorisation Safety Study (PASS), or a Post Authorisation Efficacy Study (PAES), or the study is judged to be unlikely to achieve its stated scientific purpose, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP.

Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted according to the respective legislation.

It is highly recommended that Head of Department of Risk Management and Head of Department of Clinical Research advice is sought on the design and conduct of any studies. Competent authority may ask expert opinion if necessary. The responsibility for the scientific value of study protocols remains with applicants or marketing authorisation holders, even if they have been previously discussed with our competent authority.

For some safety concerns, additional pharmacovigilance activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or

further pre-clinical work. The appropriate guidelines and legislation should be followed in the conduct of these studies.

Protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until completion of the study and submission to the competent authorities of the final study report. Changes to the protocol which do not affect milestones or due dates are not considered to be updates to the RMP.

For studies conducted as an obligation, the marketing authorisation holder shall submit the study protocol to the competent authority. For other studies, marketing authorisation should include title, the abstract of the study protocol and the abstract of the final study report.

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

#### ***2.9.2.1. Particular situations with post authorisation safety studies***

##### **a. Studies to measure the effectiveness of risk minimisation measures**

Studies looking at the effectiveness of risk minimization 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.

##### **b. Drug utilisation studies**

Drug utilisation studies are sometimes requested by national competent authorities to monitor drug usage in their country, often in relation to reimbursement discussions. However, although they may not be initiated to collect safety data, they can provide useful information on whether risk minimization activities are effective and on the demographics of target populations. If drug utilization studies aren't done, it should be included in pharmacovigilance plan.

##### **c. Joint studies**

If safety concerns apply to more than one medicinal product, the national competent authority shall encourage the marketing authorisation holders concerned to conduct a joint PASS

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. Where the PRAC agrees to impose the same PASS on more than one marketing authorisation holder and the concerned marketing authorisation holders have failed to agree a common protocol within a reasonable period of time, as determined by the PRAC, the national competent authority, with input from the PRAC, may define either a common core protocol or key elements within a protocol which the concerned marketing authorisation holders will have to implement within a timescale laid down within the request. Hence, the study would become a condition of the marketing authorisation and be reflected in the RMP. In some circumstances, the encouragement to do joint studies may relate to a single active substance where there are multiple marketing authorization holders for the same active substance.

##### **d. Registries**

Registry study should be in RMP if it is done.

#### **2.9.3. RMP part III section “Action plans for safety concerns with additional pharmacovigilance requirements”**

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

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

For each action:

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

As well as listing any additional pharmacovigilance activities under “proposed actions,” protocols (draft or otherwise) for any formal studies should be provided in RMP annex 5.

#### **2.9.4. RMP part III section “Summary table of additional pharmacovigilance activities”**

The pharmacovigilance plan describes pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions of the marketing authorisation (MA) either because they are key to the benefit-risk of the product, or because they are specific obligations in the context of a MA under exceptional circumstances [Legislation on Regulatory of Medicinal Products for Human Use, art.10 (Regulatory on Special Case) and Annex 1 (Documents for Application of Exceptional Cases)].

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

The summary table of the pharmacovigilance plan should provide clarity to all stakeholders as to which category an activity in the pharmacovigilance plan falls under, i.e.:

1. As a condition of the marketing authorization, requested post marketing authorization study by competent authority
2. In case of requested post marketing authorization safety/effectiveness study by competent authority
3. Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities;
4. Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimization activities.

**Table 2: Attributes of different Pharmacovigilance activities**

	Type of activity	Category in Summary table of Pharmacovigilance activities
As a condition of the marketing authorization, requested post marketing authorization study by competent authority	Interventional	1
	Interventional	1
In case of requested post marketing authorization safety/effectiveness study by competent authority	Interventional	2
	Non-interventional	2
Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities	Interventional	3
	Non-interventional	3
Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimization activities.	Interventional	4
	Non-interventional	4

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

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

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

Description of Activity	Expected date when results will be available

### 2.10. RMP part IV “Plans for post-authorisation efficacy studies”

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



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

Long term follow-up of efficacy as part of post-authorisation surveillance should be done for certain medicinal products namely:

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

It can be required that 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.

#### **2.10.1. RMP part IV section “Summary of existing efficacy data”**

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

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

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

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

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

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

### 2.10.2. Tables of post-authorisation efficacy studies

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

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

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

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

Other post - before MAH efficacy/effectiveness studies:

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

### 2.11. RMP Part V “Risk minimisation measures”

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

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Examples when multiple risk minimisation plans could be considered include:

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

population.

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

All risk minimisation measures should be reviewed at regular intervals and their effectiveness assessed (see 2.11.4.).

### **2.11.1. RMP part V section “Routine risk minimisation”**

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

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

The summary of product characteristics (SmPC) and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal product. The design of the packaging, and even the formulation itself, may play an important role in preventing medication error.

#### **a. Package size**

Since every pack size is specifically authorised for a medicinal product, planning the number of “dosage units” within each pack, and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of “dosage units” should mean that patients will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the length of time a patient is without review.

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 can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal product may be prescribed, or the conditions under which a patient may receive a medicinal product.

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

For medicinal products only available on prescription, additional conditions may be imposed by

classifying medicinal products into those available only upon either a restricted medical prescription or a special medical prescription.

#### Restricted medical prescription

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

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
- the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere;
- 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

The term “specialist” is usually phrased as: “treatment by a physician experienced in the treatment of <the disease>”. Although restricting to use in a hospital environment may in practice ensure that the medicinal product is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicinal product can be safely administered. For example the term “clinic” has different connotations depending upon the country. For this reason, the type of equipment needed should be specified rather than a location: e.g. “use in a setting where resuscitation equipment is available.”

#### Special medical prescription

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

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971;
- 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;
- 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.

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.

### **2.11.2. RMP part V section “Additional risk minimisation activities”**

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

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

It is essential that appropriate specialists/ experts are involved when developing risk minimisation activities.

Where appropriate, full details of additional risk minimisation activities (including mock ups) should be provided in RMP annexes 10 and 11.

### Educational material

Any educational material should be non-promotional.

The final version of the educational material will need to be approved by the national competent authority for the territory in which it will be used who will check that the material contains the key elements in an appropriate design and format and is not promotional. For public health reasons, applicants/marketing authorisation holders for the same active substance may be required by the competent authority to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorisation applicants/holder are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material.

### **2.11.3. Format of risk minimisation plan(s)**

Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed then “none proposed” should be entered against the objective. For each safety concern, the following information should be provided:

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

For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC), or a precis, should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

#### **2.11.4. RMP part V section “Evaluation of the effectiveness of riskminimisation 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 risk-benefit balance is optimised.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place. The marketing authorisation holder should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

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

#### **2.11.5. RMP part V section “Summary of risk minimisation measures”**

A table summarising the routine and additional risk minimisation activities by safety concern should be provided.

#### **2.12. RMP part VI “Summary of activities in the risk management plan”**

The summary, in total has six section, must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.

##### **2.12.1. MP part VI section “format and content of the summary of the RMP”**

This is a scientific summary, written for the lay reader to fulfil the requirements in the legislation. In situations where the RMP covers more than one product, a separate RMP part VI should be prepared for each product. To present a balanced picture, the risks discussed in the RMP should be put into context with a very concise and focussed description of the benefits of the medicinal product. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

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

- Overview of disease epidemiology;
- Summary of treatment benefits;
- Unknowns relating to treatment benefits;
- Summary of safety concerns:

- Important identified risks;
- Important potential risks;
- Missing information;

- Summary of risk minimisation activities by safety concern;
- Planned post authorisation development plan;
- Studies which are a condition of the marketing authorisation (see 2.9.4. and 2.10.2.);
- Major Changes to the Risk Management Plan over time.

The information provided in each section should be brief, focussed and in accordance with the word limits in the templates.

### **2.12.2. RMP part VI section “Overview of disease epidemiology“**

The applicant/marketing authorisation holder should summarise the epidemiology of the disease/condition the medicinal product is intended to treat or prevent (as presented in RMP module I) in a non-alarmist manner and in language appropriate to the target population. If the product is used in a range of disease severity, this fact should be emphasised and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy. If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5 year survival) figures relate to historical treatment.

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

### **2.12.3. RMP part VI section “Summary of treatment benefits”**

This should consist of very concise high level key messages concerning the results of the pivotal trials and any important supplementary evidence and should adhere to the word limits in the template.

### **2.12.4. RMP part VI section “Unknowns relating to treatment benefits”**

This should discuss the applicability of efficacy to all patients in the target population. It should describe very briefly any relevant parts of the target population where experience is limited and whether efficacy is expected to be different in these people, e.g. factors such as age, sex, race and organ impairment.

### **2.12.5. RMP part VI section “Summary of safety concerns”**

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

<b>Risk</b>	<b>What is known</b>	<b>What is known</b>
	<b>Preventability</b>	<b>Preventability</b>
Risk1		
Risk 2etc.		

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

Risk	What is known
Risk1	
Risk 2etc.	

For missing information it should be stated (using the above format as well) that there is no, or insufficient, information regarding the safety concern, the possible relevance to the target population should be highlighted as well as the associated recommendations (e.g. contraindication, use with caution).

**2.12.6. RMP part VI section “Summary of risk minimisation activities by safety concern”**

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

<p>These additional risk minimization measures are for the following risks:</p> <p><b>Blood clots (Thromboembolic events)</b></p> <p><i>Health Professional and patient education</i></p> <p><u>Objective</u> Patients and HCPs to understand the risk of occurrence of thromboembolic events and the appropriate management of the risk.</p> <p><u>Proposed actions</u></p> <ul style="list-style-type: none"> <li>• HCP educational materials to be provided to prescribing physicians and pharmacists warning about these risks and measures to take.</li> <li>• Patient booklet will inform patients what the symptoms of thromboembolic events are and the importance of seeking medical help immediately</li> <li>• Direct HCP communication prior to lunch (Dear HCP letter)</li> </ul>
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Belirli bir endikasyon veya popülasyon için güvenlik sorunlarının yaşandığı durumlarda veya ileri tedavi ürünlerinin söz konusu olduğu durumlarda, riskleri Modül VII içinde önerilen başlıklar halinde yapılandırmak uygun olur.

### 2.12.7. RMP part VI section “Planned post-authorisation development plan”

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from sections 2.9.4. and 2.10.2.. Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

*List of studies in post authorisation development plan*

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

### Studies which are a condition of the marketing authorisation

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

### 2.12.8. RMP part VI section “Summary of changes to the risk management plan over time”

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

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### 2.13. RMP part VII “Annexes

The RMP should contain the annexes listed below. Annexes 2-3, 10 and 11 should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing issues in both parts III and IV of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

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

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

- current licence status (approved/refused/ under review/
- suspended/expired/withdrawn);
- date(s) of approval/refusal/suspension/expiration/withdrawal;

- date(s) marketed/withdrawn from market;
- trade name(s);
- any explanatory comments.

RMP annex 4: Synopsis of on-going and completed clinical trial programme.

RMP annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme.

RMP annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III.

RMP annex 7: Specific adverse event follow-up forms.

RMP annex 8: Protocols for proposed and on-going studies in RMP part IV.

RMP annex 9: Synopsis of newly available study reports for RMP parts III-IV.

RMP annex 10: Details of proposed additional risk minimisation activities (if applicable).

RMP annex 11: Mock up examples of the material provided to healthcare professionals and patients if can utilised.

RMP annex 12: Other supporting data (including referenced material).

## **2.14. The relationship between the risk management plan and the periodic safety update report**

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

The PSUR examines the overall safety profile as part of an integrated benefit-risk evaluation of the medicinal product at set time periods and as such will consider the overall risk-benefit balance 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 2.8.7.2.).

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.

### **2.14.1. 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 3: Common sections between RMP and PSUR (may not be in identical format)**

RMP section	PSUR section
Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”	Section 3 – “Actions taken in the reporting interval for safety reasons”
Part II, module SV – “Post-authorisation experience”, section “Non-study postauthorisation exposure”	Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”
Part II, Module SVII – “Identified and potential risks”	Sub-section 16.4 – “Characterisation of risks”
Part II, module SVIII – “Summary of the safety concerns” (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)	Sub-section 16.1 – “Summary of safety concerns”
Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”	Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”

### 2.15. Principles for assessment of risk management plans

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

#### a. Safety specification

- Have all appropriate parts of the safety specification been included?
- Have all appropriate data been reviewed when compiling the safety specification (i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification)?
- If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
- What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicinal product?
- Are there specific risks in addition to those addressed under ICH-E2E (e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error, etc.)?
- Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?
- If known drug substance application, abridged application (generic application) first paragraph or abridged application last paragraph application have done, have all safety concerns from the reference medicinal product been included in the safety specification?
- Does its place in the therapeutic armamentarium as described concur with the intended indication and current medical practice?

#### **b. Pharmacovigilance plan**

- Are all safety concerns from the safety specification covered in the pharmacovigilance plan?
- Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
- Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?
- Are the safety studies which have been imposed by a competent authority as conditions clearly identified?
- If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
- Are the proposed additional studies necessary and/or useful?
- When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
- Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

#### **c. Plans for post-authorisation studies on efficacy**

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

#### **d. Risk minimisation measures**

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

#### **e. Summary of the Risk Management Plan**

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

#### **f. When an update is being assessed**

- Have new data been incorporated into the safety specification?
- Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?
- Is there an evaluation of the effectiveness of risk minimisation measures?
- Have appropriate changes to risk minimisation measures been proposed if necessary?
- Does the new data suggest that a formal evaluation of the risk-benefit balance (if not already done in a PSUR) is needed?

#### **2.16. Quality systems and record management**

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

### **SECTION III**

#### **Operation in Our Country**

#### **3.1. Legal basis for the implementation of risk management**

It is the legal basis for the implementation of risk management “Legislation on Safety of Medicines” dated 15.04.2014 and numbered 28973 published in the Official Gazette.

#### **3.2. Situations when a risk management plan should be submitted**

RMP or an update, as applicable, may need to be submitted at any time during a product’s lifecycle (i.e. during both the pre- and post-authorisation phases).

##### **a. During the application of MAH**

The applicant should get the confirmation before MAH procedure completed and submit RMP to competent authority for the situations given below:

1. New applications for the combination drug/medicine that contains new drug substance;
2. Application for Biotechnological Drug;
3. Application for Bioequivalent Drug;
4. Application for generic/combination drugs that are requested for additional risk minimization efficacy for original drug (e.g talidomid, isotretinoin, rituksimab, bosentan, infliximab)
5. In case of the identification of any safety concern that may require an additional pharmacovigilance or risk minimization activity at the any stage of the authorization period;
6. The authorized drugs containing new drug substance, biotechnological drugs, biosimilar drugs and generic drugs for whom the necessity of additional risk minimization activities have been identified for original drugs;
  - i. In case of application for new administration route that causes safety concern and requires additional pharmacovigilance or additional risk

minimization activities (eg; in case of marketing authorization application for sc administration of X drug which is administered by iv)

ii. In case of application for new dosage form that causes safety concern and requires additional pharmacovigilance or additional risk minimization activities

*If there is no new condition that causes safety concern and requires additional pharmacovigilance or risk minimization activities for the submission of the registered drugs containing new drug substance, biotechnological drugs, biosimilar drugs and generic drugs for whom the necessity of additional risk minimization activities have been identified for original drugs; reasons to not submit RMP should be described with the justification in CTD module 1.8.2.*

7. In case of requested by Agency.

**b. Post-authorization:**

1. In the case of using a new manufacturing process for authorized biotechnological or biosimilar drugs;
2. In case of the detection of any safety problem that may require an additional pharmacovigilance or risk minimization activity at the any stage of post-authorization;
3. In case of submitting the following changes in the license of drugs containing new drug substance, biotechnological drugs, biosimilar drugs and generic drugs for whom the necessity of additional risk minimization activities have been identified for original drugs;
  - i. Significant change that may cause safety concern or require additional pharmacovigilance or risk minimization activities in the indication: Approved indication/indications of a drug, it is the situation that the new population targeted by the treatment differs from the approved population of the drug. It includes, but not limited to, followings:
    - A new disease area.
    - A new age group (eg: indication for pediatrics).
    - Moving to the first step from the second step.
    - Change in the co-administered drug specified in the indication for an oncology drug.

*If it is thought that the conditions in this article is not conducted; reasons to not submit RMP should be described with the justification to Risk Management Department.*

4. In case of requested by Agency.

**3.3. Submission of risk management plan**

According to Regulation on Safety of Drugs Article 22(7) and this guideline; RMP should be submitted during authorization application submitted since 15.04.2014 and post-authorization for the drugs specified in Section 3.2. However; this date is not valid for biosimilar drugs according to “Guideline on Biosimilar Drug” and RMP should be submitted and approved prior to the completion of authorization process for all the biosimilar drugs.

During marketing authorization submission; when submitted the CTD dossier to Preliminary Assessment Unit, pharmacovigilance information should be included in Section 1.8. When describing the pharmacovigilance system in Section 1.8.1, RMP should be included in Section 1.8.2. When received a letter about the start of the authorization process from Preliminary Assessment Unit; a copy of this letter along with RMP should be submitted to Risk Management Department Pharmacovigilance Risk Management Unit. When

submitted to Pharmacovigilance Risk Management Unit; general information of the drug, summary table of pharmacovigilance activities conducted/to conduct in our country and summary table of risk minimization measures should be stated in the annex of cover letter. If a globally prepared RMP is submitted; a column containing activities conducted/to conduct in our country should be added to “Pharmacovigilance studies/activities table” in RMP (it should be clearly described if routine and each of additional study/activity is conducted or not in our country), a column containing activities conducted/to conduct in our country should be added to “summary table of risk minimization activities” [it should be clearly described if routine and each of additional study/activity is conducted or not (with justification) in our country; for example if there is an addition to SPC in routine activities, information about if the SPC contains this addition or not in our country and proposed/approved SPC documents should be referred]. Furthermore; updated original SPCs and proposed Turkish SPCs (submission dates and e-tracking number should be specified), if available, for the drugs should be added to the dossier.

For each applicant/marketing authorization holder; if different submissions are not requested by Agency or if same decision is made on the demands of applicant/marketing authorization holder, all drugs containing the same drug substance can be included in a single RMP [Regulation on Safety of Drugs Article 19(2)].

### **3.4.Updating the Risk Management Plan**

According to the Regulation on Safety of Drugs Article 20(1); if there is an update in the RMP plan, marketing authorization holder should submit the updated RMP (by giving a different version number and date) to Agency. Updated RMP should be submitted in clean and tracked changes version along with a new cover letter describing the changes performed from the last version. However; if the changes do not require additional pharmacovigilance or risk minimization activities, it is not necessary to submit to Agency.

Updated RMP should be submitted in the following conditions:

- On the demand of Agency
- If new information causes a significant change in the benefit/risk ratio of the drug or if reached an important pharmacovigilance or risk minimization milestones.