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Annex C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU – RMP)

This template provides advice on how the data requested in the Guideline, if available, should be presented. It is anticipated that, particularly in section 1, all the information will not be available for all drugs and that the type of product and where it is in its lifecycle will affect how much information can be provided.

Overview of EU Risk Management Plan Template	
Section	
	Product information
1	Safety Specification
2	Pharmacovigilance Plan
3	Evaluation of the need for risk minimisation activities
4	Risk Minimisation Plan
5	Summary of the EU-RMP
6	Contact person details
Annex 1	Interface between EU-RMP and Eudravigilance <i>To be provided in electronic form only</i>
Annex 2	Current (or proposed if initial EU-RMP) SPC, Package Leaflet
Annex 3	Synopsis of ongoing and completed clinical trial programme
Annex 4	Synopsis of ongoing and completed pharmacoepidemiological study programme
Annex 5	Protocols for proposed and ongoing studies in pharmacovigilance plan
Annex 6	Newly available study reports
Annex 7	Other supporting data
Annex 8	Details of proposed educational programme (if applicable)

To be valid an EU-RMP MUST contain sections 1,2 & 3. With the exception of section 4 (which must be completed if additional risk minimisation activities are proposed) all sections should be provided. Annex 1 should be provided in electronic form only.

Please ensure that the data provided in this document are coded in MedDRA terms where appropriate and are consistent with those submitted electronically in the template attached in Annex 1.

PRODUCT DETAILS

Invented name of the medicinal product (product short name):	
Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Medicinal Product Code (From EudraVigilance)	
Authorisation procedure(s) (central, mutual recognition, decentralised, national)	
Name of Marketing Authorisation Holder or Applicant:	
Date and country of first authorisation worldwide	
Date and country of first launch worldwide	
Date and country of first authorisation in the EEA	If different from above
Date and country of first launch in the EEA	If different from above

Data lock point for EU – RMP

dd/mm/yyyy

Version

Brief description of product (chemical class, mode of action etc)	
Indication(s)	Current if applicable Proposed if applicable
Dosage	Current or proposed for each indication and duration of therapy
Pharmaceutical form(s) and strength(s)	

PART I

1. SAFETY SPECIFICATION

Non-clinical

1.1.1. *<Outline of safety concerns that have not been adequately addressed by clinical data or which are of unknown significance>; for example*

Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.)

General safety pharmacology (cardiovascular [including QT interval prolongation,] nervous system, etc.)

Mechanisms for drug interactions

Other toxicity-related information or data

SAFETY CONCERN (from non clinical studies)	RELEVANCE TO HUMAN USAGE
<repeat dose toxicity>	
<reproductive toxicity> a summary of important findings(including negatives) should always be included if the drug is intended for use in women of childbearing age.	
<developmental toxicity>	
etc	

1.1.2. *<Specify need for additional non-clinical data if the product is to be used in special populations>*

Clinical

1.2 Limitations of the human safety database

1.2.1 Exposure

Clinical trial exposure

The following tables should be provided, separately for each indication with a summary table showing total exposure. Provide each table, where available, based on exposed (to medicinal product of interest) persons in:

- a) randomised, blinded trial population only
- b) all clinical trial populations (including open extension).

Table 1: BY DURATION		
INDICATION (or TOTAL)		
Duration of exposure	Persons	Person time
Cumulative Up to 1 m		
Cumulative Up to 3 m		
Cumulative Up to 6 m		
Cumulative Up to 12 m		

Table 2: BY DOSE		
INDICATION (or TOTAL)		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2		
etc		

Table 3: BY AGE GROUP AND GENDER				
INDICATION (or TOTAL)				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2				
etc				

Table 4: BY ETHNIC ORIGIN		
INDICATION (or TOTAL)		
	Persons	Person time
Ethnic origin 1		
Ethnic origin 2		
etc		

Table 5: SPECIAL POPULATIONS		
INDICATION (or TOTAL)		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism (specify)		

Note the categories provided, are suggestions only and the tables should be tailored to the product, clearly identified and justified. For example, for parenteral administration, consider number of administrations e.g. 1, 2, 3 or more repeated exposures. For age and gender make explicit reference to paediatric and elderly populations.

Epidemiological study exposure

Study	Study type (eg cohort or case/control)	Population studied	Duration (study period)	Number of persons (in each group or of cases and controls)	Person time (if appropriate)
Study1					
Study 2					
etc					

Post marketing (non study) exposure

Data on patients exposed post marketing should be provided based on market research where possible. When the number of persons is calculated on the basis of sales data, details and justification should be provided of the measure used to calculate exposure. Tables should be provided for each indication where possible.

Table 1: BY AGE GROUP AND GENDER				
Indication				
Age group	Persons		Exposure (eg packs or person years)	
	M	F	M	F
Age group 1				
Age group 2				
etc				

Table 2: BY DOSE		
Indication		
	Persons	Exposure (eg packs or person years)
Dose level 1		
Dose level 2		
etc		

Table 3: BY COUNTRY		
Indication		
	Persons	Exposure (eg packs or person years)
EU		
Non-EU		

If possible, EU use should be broken down into country or sales area. Note the categories provided, are suggestions only and other relevant variables can be used eg oral versus iv, duration of treatment etc.

1.3 Populations not studied in the pre-authorisation phase

For each pivotal and supporting study, list exclusion criteria for studies.

Study number	No of patients exposed to this product in the study	Age range	Exclusion criteria for study

The limitations of the human safety database should be discussed in terms of the relevance of inclusion and exclusion criteria and the populations actually studied in relation to the target population(s). Where exclusion criteria are not proposed as contraindications to treatment this should be discussed and justified. Populations to be considered for discussion should include (but is not limited to):

Children

Elderly

Pregnant of lactating women

Patients with relevant co-morbidity such as clinically significant renal, hepatic or cardiac impairment

Patients with disease severity different from that studied in clinical trials

Sub-populations with genetic polymorphisms

Patients of different ethnic origins

1.4 Post authorisation experience

1.4.1. <Projected post-authorisation usage data>

For the initial EU-RMP, or when seeking a significant change to the indication, provide details on projected pattern, estimated population drug usage over time, place in treatment and market position.

1.4.2. <Actual post-authorisation usage data>

For updates to the EU-RMP, specific reference should be made to how the realised pattern of exposures has differed from that predicted, including off label use.

1.4.3. <Regulatory action taken>

For updates to the EU-RMP only, please list regulatory action taken (worldwide cumulative table)

Issue	Country	Action taken	Date
Issue 1	Country 1	Action 1	Date 1
	Country 2 etc	Action 2 etc	Date 2 etc
Issue 2 etc	Country 1 etc		

1.5 Adverse events/Adverse reactions

1.5.1. Newly identified safety concerns (since EU-RMP last submitted)

<p>Safety concern 1</p> <p>Details</p> <p>Source</p> <p>Implications for product literature</p> <p>New studies proposed in pharmacovigilance plan? Yes/No</p> <p>New risk minimisation actions proposed? Yes/No</p>
Safety concern 2 etc

1.5.2. Details of important identified and potential risks (including newly identified)

For each important identified and potential risk provide the following if available:

Identified Risk <>	MedDRA PT terms
Seriousness/outcomes	<tabulate the distribution of outcomes e.g. % fatal, % recovered/with/without treatment/sequelae, % not recovered, % hospitalised etc>
Severity and nature of risk	<e.g. tabulate grades of severity where available>
Frequency with 95 % CI	<p><as per the guideline section 4.5.2.3: give relative and excess (over placebo or comparator) as incidence rates and incidence risk for populations:</p> <p>1) randomised, blinded trial population only</p> <p>2) all clinical trial populations (including open extension)</p> <p>3) epidemiological studies stratified by indication</p> <p>Where there are clear differences in rates between populations, this should be discussed></p>
Background incidence/prevalence	Background incidence/prevalence in the target population(s)
Risk groups or risk factors	<describe use, dose, time and susceptibility data or other factors where available. Cumulative hazard function may be provided>
Potential mechanisms	<describe>
Preventability	<provide data on predictability or preventability of ADR>
Potential public health impact of safety concern	<describe or enumerate if possible, using e.g. Numbers Needed to Harm and/or expected number of patients affected, hospitalisations, fatalities given in the predicted population use>
Evidence source	<identify and cross refer to supporting data in CTD or annex data> or PM clinical trials, safety studies, pharmacoepidemiological studies, PSUR, other safety reports etc.
Regulatory action taken	<country, type of action>

1.6 Identified and potential interactions with other medicinal products, food and other substances

For each important interaction, provide the following:

Interacting substance	<>
Effect of interaction (including MedDRA terms if appropriate)	
Evidence source	<>
Possible mechanisms	<>
Potential health risk	<>
Discussion	

1.7 Epidemiology of the indication(s) and important adverse events

1.7.1. For each indication, discuss the incidence, prevalence, mortality and demographic profile of the target population

Indication/target population	<>
Incidence of target indication	<> (note if specific inter-country variation is known)
Prevalence of target indication	<>
Mortality in target indication	<>
Potential health risk	<> (note if specific inter-country variation is known)
Demographic profile of target population	<Provide age sex distribution>

1.7.2. For each indication, discuss the important co-morbidity in the target population

Indication/target population	List important co-morbidity in the target population. <i>For each important co-morbidity, provide incidence, prevalence and mortality in the target population and main co-prescribed medicinal products</i>
<>	<>

1.7.3. For each identified or potential risk e.g. hepatic failure, provide the epidemiology of the condition in the target population when unexposed to the product

Identified or potential risk	<>
Incidence of condition	<>
Prevalence of condition	<>
Mortality of condition	<>

1.8 Pharmacological class effects

Identify risks which are believed to be common to the pharmacological class. If a risk which is common to the pharmacological class is not thought to be a safety concern with the medicinal product this should be justified and supporting evidence provided.

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class (source of data/journal reference)	Comment
Risk 1		Product A Product B Product C Review of adverse reactions BMJ 2008; 5; 214-217	
Risk 2 etc			

1.9 Additional EU Requirements

1.9.1. Potential for overdose

1.9.2. Potential for transmission of infectious agents

1.9.3. Potential for misuse for illegal purposes

1.9.4. Potential for off-label use

1.9.5. Potential for off-label-paediatric use

1.10 Summary – Ongoing safety concerns

Important identified risks	<.> List
Important potential risks	<.> List
Important missing information	<.> List

2. PHARMACOVIGILANCE PLAN

The pharmacovigilance plan covers the actions intended to identify and characterise safety concerns. It should not include actions intended to reduce or prevent risks.

2.1 Routine pharmacovigilance practices

Briefly summarise the routine pharmacovigilance system. If the application is via the centralised procedure please cross refer to the section in Module 1.

2.2 Summary of safety concern and planned pharmacovigilance actions

For each safety concern, provide a summary table of planned pharmacovigilance actions. Include newly available results for updates to the pharmacovigilance plan. Where no action beyond routine pharmacovigilance is planned, please justify.

Safety concern	Planned action(s)
Important identified risks	<> List
Important potential risks	<> List
Important missing information	<> List

2.3 Detailed action plan for specific safety concerns

For each important identified or potential risk or missing information, provide the following:

Safety concern	<>
Action(s) proposed	<>
Objective of proposed action(s)	<>
Rationale for proposed action(s)	<>
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	<>
Milestones for evaluation and reporting including justification for choice of milestones	<>

Titles of protocols (Annex full study protocols and provide cross reference to position in annex 5)	< >
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2.4 Overview of study protocols for the pharmacovigilance plan

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data

2.5 For updates to the EU-RMP

Safety concern	Summary of newly available results (attach study report as an annex and provide cross reference)	Implications of all available data for safety concern
Important identified risks	< > List	< > List
Important potential risks	< > List	< > List
Important information missing	< > List	< > List

2.6 Summary of outstanding actions, including milestones

Present list of actions to be completed (ongoing and planned) with milestones and timelines.

Actions	Milestones/exposure	Milestones/calendar time	Study status

PART II

3. EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES

The evaluation of the need for risk minimisation activities should list all safety concerns presented in section 1.10. Evaluate and justify whether routine (ie product information, labelling and packaging) risk minimisation activities will be sufficient or whether additional risk minimisation activities (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes) will be required. If additional risk minimisation activities are necessary a risk minimisation plan should be provided (see section 4). If, for any safety concern, no risk minimisation activities at all are proposed this should be fully justified.

3.1 For each safety concern from section 1.10, provide a summary table of planned actions

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Important identified risks (List)	Yes/No	
Important potential risks (List)	Yes/No	
Important missing information (List)	Yes/No	

3.2 Potential for medication errors

MAAs/MAHs are encouraged routinely to consider the likelihood of medication errors. In particular, they should assess prior to marketing, common sources of medication errors. During the development phase and during the design of the medicinal product for marketing, the applicant needs to take into account potential reasons for medication error. The naming (taking into account the “Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure. CPMP/328/98”), 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 life-threatening potential 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.

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. 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.

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

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

4. RISK MINIMISATION PLAN

For each important identified or potential risk for which **additional** risk minimisation measures are planned, provide the following:

Safety concern	
<i>Routine risk minimisation activities</i> (i.e. product information, labelling and packaging)	<Short description of what will be put in the SPC, labelling etc to minimise risk e.g. warning in 4.4 that caution should be used in patients with cardiac failure etc>
<i>Additional risk minimisation activity 1</i> (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes)	<i>Objective and rationale</i>
	<i>Proposed actions</i>
	<i>Criteria to be used to verify the success of proposed risk minimisation activity</i>
	<i>Proposed review period</i>
<i>Additional risk minimisation activity 2 etc</i>	<i>Objective and rationale</i>
	<i>Proposed actions</i>
	<i>Criteria to be used to verify the success of proposed risk minimisation activity</i>
	<i>Proposed review period</i>

5. SUMMARY OF THE EU RISK MANAGEMENT PLAN

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Safety concern 1	E.g. <ul style="list-style-type: none"> • routine pharmacovigilance • drug utilisation study to investigate 	E.g. <ul style="list-style-type: none"> • contraindication in section 4.3 of the SPC • warning in section 4.4 of the SPC that..... • Educational material • Controlled distribution
Safety concern 2 etc		

6. CONTACT PERSON FOR THIS EU-RMP

Names	<>
Position	<>
Qualifications	<>
Signature	<>

ANNEXES

List of annexes

Annex No	
1	Interface between EU-RMP and EudraVigilance (<i>to be provided in electronic format</i>)
2	Current (or proposed if initial EU-RMP) SPC, Package leaflet
3	Synopsis of ongoing and completed clinical trial programme
4	Synopsis of ongoing and completed pharmacoepidemiological study programme
5	Protocols for proposed and ongoing studies from Pharmacovigilance Plan
6	Newly available study reports
7	Other supporting data
8	Details of proposed educational programme (if applicable)

Examples of annexes include the following:

Annex I: Interface between EU-RMP and EudraVigilance

EU Risk Management Template: Data Elements to be provided in Electronic Format for Centrally Authorised Medicinal Products

As part of the EU Risk Management Plan it is important to monitor the identified or potential risks in the context of the suspected adverse reactions reported to EudraVigilance. This applies to centrally authorised medicinal products.

To allow the identified and potential risks to be monitored in EudraVigilance, these elements should be provided electronically. A template for capturing the relevant data elements will be provided at the EudraVigilance website (<http://eudravigilance.emea.europa.eu>) to coincide with the release of Volume 9A in one of the following formats:

- Access Database
- Microsoft Word Macros Enabled

For centrally authorised medicinal products the completed template should be provided at the initial submission of the EU Risk Management Plan and each time the plan is updated, with regard to the data elements captured in the template.

Annex 3: Ongoing & completed clinical trial programme

Study	Description, Countries	Phase,	Design, No of patients Follow-up	Estimated/Actual completion date
<i>Large outcome studies</i>				
Study ABC	Short description of study (1 – 2 sentences including comparator name(s)/placebo) Phase III Germany, USA, Chile		Double-blind 4000 1 year	Jan 2005
Study DEF	Etc		Double-blind 2000 1 year	Feb 2008
<i>Further safety/efficacy studies of XYZ</i>				
Study GHI	Etc		Double-blind 1000 26 weeks	March 2005
Study JKL	Etc		Open-label 2000 48 weeks	Nov 2005
<i>Studies in special subgroups</i>				
Study MNO	Etc		Open-label 1000 12 weeks	Feb 2005
<i>Paediatric studies</i>				
Study PQR	Etc		Open-label 500 48 weeks	Feb 2005

Annex 4: Pharmacoepidemiological programme

Study	Description	Study designs No of patients Duration of follow-up	Estimated/actual completion date (dates when interim and final study reports are expected)