

Structure of the risk management plan

Detailed description of each part of the risk management plan

Part I	Product overview.	
	1- Active substance information:	
	- Active substance(s).	
	- Pharmacotherapeutic group(s) (ATC code).	
	- Name of marketing authorization holder or applicant.	
	- Date and country of first authorization worldwide (if applicable).	
	- Date and country of first launch worldwide (if applicable).	
	- Number of medicinal product(s) to which this RMP refers.	
	2- 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.	
	3- 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 biological, relevant adjuvants or residues for vaccines);	
	4- Indications: (current and proposed).	
	5- Dosage: (current and proposed).	
	6- Pharmaceutical forms and strengths: (current and proposed).	
Part II	Safety specification:	
	Module SI: “Epidemiology of the indications and target population”	
	- The epidemiology of the indication(s) include (incidence, prevalence, mortality and relevant co-morbidity, concomitant medication), stratified by age, sex, and racial and/or ethnic origin.	
	Module SII: “Non-clinical part of the safety specification”	
	- Toxicity for <u>active substance and its impurities</u> (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.	

	Module SIII: “Clinical trial exposure” (tables/ graphs)	
	- Type of trial and number of patients.	
	- Age and gender.	
	- Indication and dose.	
	- Racial origin.	
	- Duration of exposure.	
	- The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised).	
	Module SIV: “Populations not studied in clinical trials” (Limitations and exclusion criteria) <u>Populations to be considered for discussion should include (but might not be limited to)</u>	
	- Paediatric population (under 18 years).	
	- Elderly population (over 65 years).	
	- Pregnant or breast-feeding women.	
	- Patients with hepatic/ 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.	
	- Sub-populations carrying known and relevant genetic polymorphism.	
	- Patients of different racial and/or ethnic origins.	
	Module SV: “Post-authorization experience”	
	- Action taken by regulatory authorities and/or marketing authorization holders for safety reasons (a restriction to the approved indication, a new contra-indication, a new or strengthened warning or any action to suspend or revoke a marketing authorization). (List should be cumulative, and specify the country, action taken and the date as appropriate)	
	1- Non-study post-authorization exposure (patients exposed post-marketing stratified by age, sex, indication, dose and region).	
	2- Post-authorization use in populations not studied in clinical trials.	
	3- Post-authorization off-label use.	
	4- Epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilization or measure effectiveness of risk minimization measures.	

	Module SVI: “Additional requirements for the safety specification”	
	- Potential for harm from overdose (whether intentional or accidental).	
	- Potential for transmission of infectious agents (vaccines).	
	- Potential for misuse for illegal purposes.	
	- Potential for medication errors (wrong patient, wrong medication, wrong dose, wrong route of administration).	
	- Potential for off-label use.	
	- Specific paediatric issues (follow up of safety or efficacy issues in relation to paediatric use and potential for paediatric off-label use).	
	Module SVII: “Identified and potential risks”	
	- Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.	
	- The source of the safety concern should be stated (clinical development, post-authorization experience, identified and potential interactions including food-drug and drug-drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.	
	Module SVII: “Identified and potential risks advanced therapy medicinal products” (ATMP version)	
	- Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.	
	- The source of the safety concern should be stated (clinical development, post-authorization experience, identified and potential interactions including food-drug and drug-drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.	
	<u>The additional risks specific to ATMPs which should be considered for discussion include:</u> - Risks to living donors. - Risks to patients related to the storage and distribution of the product. - Risks to patients related to administration procedures. - Risks related to interaction of the product and the patient (immunogenicity e.g. anaphylaxis, graft rejection). - Risks related to persistence of the product in the patient. - Risks related to re-administration. - Specific parent-child risks.	

	Module SVIII: “Summary of the safety concerns” tables	
	- Important identified risk. - Important potential risk. - Missing information.	
Part III	Pharmacovigilance plan	
	Structure plan for: - The identification of new safety concerns. - Further characterization of known safety concerns. - The investigation of whether a potential safety concern is real or not. - How missing information will be discussed.	
	1- Routine pharmacovigilance activities.	
	2- Additional pharmacovigilance activities. (Pharmacokinetics studies, drug utilization studies, studies to measure the effectiveness of risk minimization measures, non-interventional studies, pharmacoepidemiology studies). - Action plans for safety concerns with additional pharmacovigilance requirements. - Summary table of additional pharmacovigilance activities.	
Part IV	Plans for post-authorization efficacy studies.	
	- The medicines authority may require post-authorization 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.	
	1- Summary of existing efficacy data.	
	2- Tables of post-authorization efficacy studies (description of study, milestones, due date).	
	Note: The requirement for efficacy studies post authorization refers solely to the current indication(s) and not to studies investigating additional indications.	
Part V	Risk minimization measures.	
	1- Routine risk minimization.	
	- Summary of product characterizations and package leaflet.	
	- Pack size and labeling.	
	- Legal status of the product (restricted and special medical prescription).	

	2- Additional risk minimization activities. (only agreed by the medicines authority)	
	- Direct healthcare professional communications.	
	- Educational materials (patient alert cards and monitoring cards).	
	- Controlled distribution systems.	
	3- Evaluation of the effectiveness of risk minimization activities.	
	4- Summary of risk minimization measures (table).	
Part VI	Summary of activities in the risk management plan by medicinal product. (tables)	
	1- Summary of safety concerns.	
	- Important identified risks.	
	- Important potential risks.	
	- Missing information.	
	2- Summary of risk minimization measures by safety concern.	
	3- Planned post-authorization development plan (studies).	
	4- Summary of changes to the risk management plan over time.	
Part VII	Annexes to the risk management.	
	Annex 1	
	- Interface between RMP and —National Pharmacovigilance and Safety reports database/National Pharmacovigilance Issues Tracking Tool" (electronic only), applicable only in some Arab Countries hence this annex should be submitted only upon request from the medicines authority of the Arab Countries concerned. Further details will be announced by authorities who require such annex. In Arab Countries who do not require this annex, it should be omitted (WITHOUT changing the numbering of the following annexes).	
	Annex 2	
	- Current summary of product characteristics (SmPC) and package leaflet.	
	Annex 3	
	- Worldwide marketing authorization status by country (approved/ refused/ suspended/ withdrawn/ marketed/ not marketed).	
	Annex 4	
	- Synopsis of on-going and completed clinical trial programme.	

	Annex 5	
	- Synopsis of on-going and completed pharmacoepidemiological study programme.	
	Annex 6	
	- Protocols for proposed and on-going studies in the section Summary table of additional pharmacovigilance activities in RMP part III.	
	Annex 7	
	- Specific adverse event follow-up forms.	
	Annex 8	
	- Protocols for proposed and on-going studies in RMP part IV.	
	Annex 9	
	- Synopsis of newly available study reports for RMP parts III-IV.	
	Annex 10	
	- Details of proposed additional risk minimization activities (if applicable).	
	Annex 11	
	- Mock up examples in English of the material provided to healthcare professionals and patients. For those materials directed to patients, in addition to the English version, Arabic translation of the mock up shall be included as well.	
	Annex 12	
	- Other supporting data (including referenced material).	

Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Generic medicine	✓								✓	*	*	✓	*	✓
MAH/ Applicant having Eu RMP	✓								✓ ^①				✓ ^②	✓ ^③

* *Modified requirement.*

① *Table.*

② *Activities included in the referenced EU RMP*

Supplementary activities on the national level

- *Supplementary national pharmacovigilance activity(s)*
- *Supplementary national post-authorization efficacy study(s)*
- *Supplementary national risk minimization activity(s)*

③ *Annex (1, 2, 6, (7 to 12)).*