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Module V

Risk Management Systems

Version 1.0

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List of Abbreviations

CTD:	Common Technical Document
eCTD:	Electronic Common Technical Document
LSR:	Local Safety Responsible
MAA:	Marketing Authorization Applicant
MAH:	Marketing Authorization Holder
PAES:	Post-Authorization Efficacy Study
PSUR:	Periodic Safety Update Report
RMP:	Risk Management Plan
RMS:	Risk Management System

V.A. Introduction

A medicinal product is authorized on the basis that, in the specified indication(s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population.
However, at the time of authorization, information on the safety of a medicinal product is limited due to the relatively restricted trial population in terms of subject numbers, age, gender, and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, and the relatively short duration of exposure and follow-up. The risk-benefit balance of a medicinal product as assessed at the time of authorization will therefore inevitably change post-authorization.
Consequently, Marketing Authorization Applicants (MAAs) are encouraged to define, from very early on, in a product's life cycle, their Risk Management System (RMS) that will characterize and minimize the risks associated with the product in the post-authorization phase. A detailed description of the RMS is included in the Risk Management Plan (RMP).

To this end, the Risk Management System RMS has three stages, which are interrelated:

- "Safety specification": characterization of the safety profile of the medicinal product;
- "Pharmacovigilance plan": the planning of pharmacovigilance activities to characterize risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product;
- "Risk minimization plan": the planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities.

V.B. Structures and processes

V.B.1. Terminology

Risk Management System (RMS):

A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions.

Risk Management Plan (RMP):

A detailed description of the risk management system.

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.

Important identified risk:

From the identified risks of the medicinal product, the RMP should focus only on the important identified risks with both of the following criteria met:

1. **Identified**: these are undesirable clinical outcomes for which there is **sufficient** scientific evidence that they are caused by the medicinal product. Examples include:
    - An undesirable clinical outcome adequately demonstrated in non-clinical studies and confirmed by clinical data;
    - An undesirable clinical outcome 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 undesirable clinical outcome suggested by a number of well-documented spontaneous reports -including published literature- where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions. In a clinical trial, the comparator may be a placebo, an active substance, or non-exposure.
    - They may be linked to situations such as off-label use, medication errors, or drug interactions.

2. **Important**: these are undesirable clinical outcomes that are likely to have an **impact on the risk-benefit balance of the product**. i.e., would usually warrant:
    - Further evaluation as part of the pharmacovigilance plan (e.g., to investigate frequency, severity, seriousness, and outcome of this risk under normal conditions of use, which populations are particularly at risk);
    - Risk minimization activities: product information advising on specific clinical actions to be taken to minimize the risk, or additional risk minimization activities.

Important potential risk:

From the potential risks of the medicinal product, the RMP should address only the important potential risks with both of the following criteria met:

1. **Potential**: these are undesirable clinical outcomes for which there is scientific evidence for suspicion of the possibility of a causal relationship with the medicinal product, but where this association has not been confirmed. Examples include:
    - Non-clinical toxicological findings that have not been observed or resolved in clinical studies;
    - Undesirable clinical outcomes observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship;
    - A signal arising from a spontaneous adverse reaction reporting system;
    - An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.
    - A scientific rationale for an undesirable clinical outcome that might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product.
2. **Important**: these are undesirable clinical outcomes when further characterized and, if confirmed, would have an impact on the risk-benefit balance of the medicinal product. And would usually require further evaluation as part of the pharmacovigilance plan.

Missing information:

Gaps in knowledge about a medicinal product, related to the safety of a medicinal product for certain anticipated utilization (e.g., long-term use) or for use in particular patient populations, which could be clinically significant and for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g., exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

Safety concern:

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

Target population (treatment):

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

V.B.2. Responsibilities for risk management within an organization

The principal stakeholders directly involved in medicinal products' risk management planning are Marketing Authorization Holders (MAHs)/MAAs, and the national competent authority, who regulate this process. (see section V.C.1).

V.B.3. 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.
The appropriate planning of a RMS throughout a medicinal product's lifecycle can put risks into context and therefore enable better resource allocation.

The RMP is a dynamic document that should be updated throughout the life cycle of the product(s). This includes:

- The addition of safety concerns where required;
- Important potential risks can be:
    - Removed from the safety specification in the RMP, e.g.:
        - When accumulating scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated, resulting in the potential risk not being considered important; or
        - When there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk, or

- Reclassified to “important identified risks” (e.g., if scientific and clinical data strengthen the association between the risk and the product);

- Important identified risks may be:
  - Removed from the safety specification (e.g., for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimization recommendations have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines;
- Missing information might not be appropriate anymore once new data becomes available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information;
- Additional pharmacovigilance activities in the RMP (with the exception of some patient registries) it is expected that over time they will be completed and thus removed from the RMP;
- Additional risk minimization activities may be:
  - Removed: as the risk minimization recommendations for specific clinical measures to address the risk become part of the routine practice, such as inclusion into standard treatment protocols;
  - Replaced: in response to the findings of effectiveness of risk minimization evaluations (i.e., they may need to be replaced with more effective activities);
  - Retained for the lifetime of the medicinal product (e.g., pregnancy prevention programs).

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

A RMP must fulfil the following obligations:

- Describing what is known and not known about the safety profile of the concerned medicinal product(s);
- Characterizing the safety profile of the medicinal product(s) concerned;
- Indicating how to further characterize the safety profile of the medicinal product(s) concerned;
- Documenting measures to minimize the risks associated with the medicinal product, including a description and an assessment of the effectiveness of those interventions;
- Documenting post-authorization obligations that have been imposed as a condition of the marketing authorization.

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

The RMP is a dynamic, stand-alone document that should be updated throughout the life cycle of the products. It consists of seven parts in a modular structure to allow easy tailoring of the sections to the specifics of the medicinal product(s). RMP modules can be added/removed as appropriate as the product matures. The amount of information which can be provided will depend on the type of medicinal product, where it is in its lifecycle, and is proportionate to the product's important identified risks and the important potential risks. Information should be provided in enough detail to enable an assessor to understand the issues being presented.

The following is an overview of the RMP content:

Part I: Product(s) overview

Part II: Safety specification

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

Part III: Pharmacovigilance plan

Part IV: Plans for post-authorization efficacy studies

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)

Part VI: Summary of the risk management plan

Part VII: Annexes

It is recommended, where appropriate, that the RMP document include all relevant medicinal products containing the same active substance(s) from the same MAH/MAA (i.e., the RMP is an active substance-based document).

Unless specifically mentioned in this guidance, cross-references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document that is a scientific synopsis of the relevant parts of the dossier, emphasizing the important clinically relevant facts.

The MAH must explicitly refer to and utilize the RMP EU module and the EU RMP template or the mother country-based RMP. (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans) throughout the development of the RMP. Compliance with this essential directive is vital to ensure and promote the development of a comprehensive and compliant RMP for the medicinal product.

Below is an overview of the parts and modules to be included in the RMP.

V.B.5.1. RMP Part I: Product overview

Part I of the RMP provides administrative information on the RMP and an overview of the product(s). This includes:

- 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 the RMP was last submitted. and for each medicinal product included in the RMP.

V.B.5.2. RMP Part II: Safety specification

Part II of the RMP provides a synopsis of the safety profile of the medicinal product(s). It should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information (see section V.B.1). It should also address the populations potentially at risk.

The safety specification consists of eight RMP modules that will form the basis of the pharmacovigilance plan and the RMP.

V.B.5.3. RMP Part III : Pharmacovigilance plan

Part III of the RMP discusses how the MAH/MAA plans to confirm, characterize, and investigate the risks identified in the safety specification. Actions intended to reduce, prevent, or mitigate these risks are discussed in RMP Part V.

For each safety concern, the MAH/MAA should list its planned pharmacovigilance activities for that concern. Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities.

V.B.5.4. RMP Part IV: Plans for post-authorization efficacy studies

Part IV of the RMP offers a concise overview of the need for Post-Authorization Efficacy Studies (PAES), particularly for pediatric and advanced therapy medicinal products, addressing post-marketing concerns and adapting to evolving disease knowledge, while outlining essential study components. For most medicines, there will not be a need for post-authorization 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 authorization is necessary. For pediatric medicinal products and advanced therapy medicinal products, there may be a potential need for long-term follow-up of efficacy as part of post-authorization surveillance for certain medicinal products.

V.B.5.5. RMP Part V: Risk minimization measures

Each safety concern identified in the safety specification (Part II) should be addressed by one or more risk minimization measures aiming to reduce the associated risk. This will depend on the severity of the risk, the healthcare setting, the indication, the pharmaceutical form, and the target population. These measures may consist of routine risk minimization or additional risk minimization activities. For each risk minimization measure, the objective, evaluation, criteria for success, and milestones should be provided.

V.B.5.6. RMP Part VI: Summary of activities in the risk management plan

A summary of the RMP for each medicinal product should be provided and should include the key elements of the RMP assembled in table format in a brief and focused manner. Where a RMP concerns more than one medicinal product, a separate RMP Part VI must be provided for each medicinal product.

V.B.5.7. RMP Part VII: Annexes to the risk management plan

When applicable, the RMP should include several annexes.

V.B.6. Types of activities in the risk management plan

V. B. 6. 1 Pharmacovigilance plans

Those are the activities designed by the MAH/MAA for:

- The investigation of whether an important potential risk is confirmed as an important identified risk or refuted;
- Further characterization of safety concerns, including severity, frequency, and risk factors;
- How missing information will be sought;

For each safety concern, the MAH/MAA should consider the need for pharmacovigilance activities. Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities.

Routine pharmacovigilance activities:

These are the primary/minimum set of activities required for all medicinal products. The types of these activities and the scope for inclusion in the RMP are described below:

- Adverse reaction reporting: already described in the PSMF and is not required to be repeated in the RMP;
- Signal detection: already described in the PSMF and is not required to be repeated in the RMP.

RMP section on "Pharmacovigilance plan" should describe only those routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

In certain situations, the national competent authority in Lebanon 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.

- If these requirements include recording of tests as part of normal clinical practice for a patient experiencing the adverse reaction, then this requirement would be considered as routine pharmacovigilance activity.

- If the recommendation includes the submission of tissue or blood samples to a specific laboratory that is outside the normal clinical practice, then this would constitute an additional pharmacovigilance activity.

- Specific adverse reaction follow-up questionnaires:
  Used when a MAH/MAA is requested, or plans to use specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest. Such questionnaires used by different MAHs/MAAs for the same adverse event should be kept as similar as possible.
- Other forms of routine pharmacovigilance activities:
  Examples: the high-level description of the enhanced passive surveillance system, observed versus expected analyses, and cumulative reviews of adverse events of interest.

Additional pharmacovigilance activities:

These are not considered routine. Their objective 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, to assess a causal association, to provide long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterization of the long-term safety of the medicinal product. 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.

Such studies may be:

- Non-clinical studies; or
- Clinical trials; or
- Non-interventional studies.

(This section should be read in conjunction with Module VIII on Post-Authorization Safety Studies).

V. B. 6. 2 Risk minimization measures

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

1. **Routine risk minimization activities:**

Apply to every medicinal product and relate to the following:

- Summary of Product Characteristics (SmPC) and the package leaflet:
  These are standardized tools to inform healthcare professionals and patients about the product. Both materials provide routine risk minimization recommendations; however, there are two types of messages
  - routine risk communication messages: e.g., sections on undesirable effects
  - routine risk minimization activities recommending specific clinical measures to address the risk e.g., sections on warning and precaution, contraindication, interactions, fertility, pregnancy and lactation, ability to drive and overdose.
- Pack size:
  Controlling the number of dosage units allows for regular check-ups by a healthcare professional and thus a better control of the patient.
- Legal status:
  The legal status of a product is the condition under which a medicinal product is made available (need for a prescription, setting of administration…). Controlling the legal status of a product can reduce the risk associated with its use.

2. **Additional Risk Minimization activities**

Such activities are mainly communication tools used to augment information in the SmPC and the package leaflet and targeting patients and healthcare professionals.
Educational material provided as additional risk management measures should be non-promotional. The content of such material should be reviewed and approved by the national competent authority, and it will be a condition of the marketing authorization. MAHs/MAAs for the same active substance are required to use similar educational material to avoid patient confusion. Company logos should therefore be avoided.
Further guidance on the additional risk minimization measures is provided in Module XVI.

V.B.7. Relationship between the risk management plan and other pharmacovigilance documents

V.B.7.1 Risk Management Plan and the Common Technical Document (CTD)

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 summarized for the RMP.

To note that in Lebanon, where the Electronic CTD (eCTD) is not yet applied, the RMP should be submitted as a PDF file (text) on a CD along with the submission application or submission cover letter, adhering to national requirements. Once the eCTD becomes a legal requirement, the RMP will be submitted as PDF files within the eCTD submission.

Table 1: Mapping between RMP Modules and CTD

	RMP	**CTD**
	- The RMP is part of the scientific dossier of a product. - The RMP should provide an integrated overview focusing on the most important risks identified based on data presented in other modules of the CTD.	
Content	Part I: Product(s) overview	Module 2.3: Quality overall summary Module 3: Quality
	Part II: Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5: Clinical overview
	Module SII: Non-clinical part of the safety specification	Module 2.4: Non-clinical overview Module 2.6: Non-clinical written and tabulated summaries Module 4: Non-clinical study reports
	Module SIII: Clinical trial exposure	Module 2.7: Clinical summary Module 5: Clinical Study Reports
	Module SIV: Populations not studied in clinical trials Module SV: Post-authorization experience	Module 2.5: Clinical overview
	Module SVII: Identified and potential risks Module SVIII: Summary of the safety concerns Part III: Pharmacovigilance plan Part IV: Plans for post-authorization efficacy studies Part V: Risk minimization measures	Module 2.7: Clinical summary

V.B.7.2. Risk Management Plan (RMP) and the Periodic Safety Update Report (PSUR)

The primary post-authorization pharmacovigilance documents for safety surveillance are 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 retrospective, integrated, post-authorization risk-benefit assessment, whilst that of the RMP is prospective pre-and post-authorization risk-benefit management and planning. As such, the two documents are complementary. When a PSUR and an RMP are 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 to be added in the RMP, the important risk can be added in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimization plan should be updated to reflect the MAH's proposals to further investigate the safety concern and minimize the risk.

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

Table 2: Comparison of RMP and PSUR Characteristics and Their Common Components

	RMP	**PSUR**
Objective	Prospective pre-and post-authorization risk-benefit management and planning	Retrospective, integrated, post-authorization risk-benefit assessment
Submission	One or both, depending on the product lifecycle stage	
Content	Despite the differences, there might be overlap; complementary stand-alone documents	
Common content (sections)	Part II, module SIII – "Clinical trial exposure"	Sub-section VII.B.5.5.1- "Cumulative subject exposure in clinical trials"
	Part II, module SV – "Post-authorization experience"	Sub-section VII.B.5.5.2 - "Cumulative and interval patient exposure from marketing experience"
	Part II, module SVII – "Identified and potential risks" and Part II, module SVIII – "Summary of the safety concerns"	Sub-sections VII.B.5.16.1- "Summaries of safety concerns" and VII.B.5.16.4 "Characterization of risks"
	Part V – "Risk minimization measures", section "Evaluation of the effectiveness of risk minimization activities"	Sub-section VII.B.5.16.5 - "Effectiveness of risk minimization (if applicable)"

V.C. Operations of risk management in Lebanon

V.C.1. Responsibilities of marketing authorization holders/applicants

The principal stakeholders directly involved in medicinal products' risk management planning are MAHs/MAAs and the national competent authority.

Producing an RMP requires the involvement of different specialists within or outside the organization, including clinical research physicians, toxicologists, clinical pharmacologists, and pharmacoepidemiologists. Since an RMP is primarily a pharmacovigilance document, its production should be managed by personnel with appropriate training in either the pharmacovigilance or regulatory departments.

In relation to risk management, the MAH/MAA is responsible for:

- Having an appropriate risk management system in place;
- Ensuring that the knowledge and understanding of the product's safety profile, following its use in clinical practice, are critically reviewed. The MAH should monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed, or whether there are changes to the risk-benefit balance of medicinal products;
- Updating the RMS and the RMP according to updates in the product's safety profile and RMP activities;
- Taking all appropriate actions to minimize the risks of the medicinal product and maximize the benefits by 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.

V.C.2. Submission of the risk management plan

The RMP or an update of the RMP can be submitted at any time during a product's life-cycle, i.e., during both the pre- and post-authorization phases, generally as a PDF file.

For new marketing authorization applications, the initial RMP should be submitted as part of the initial marketing authorization within the CTD submission.

Additional situations where submission of the RMP is expected include:

- When there is a significant change to an existing marketing authorization (new dosage form, new route of administration, new manufacturing process, pediatric indication);
- When there is a concern about a risk affecting the risk-benefit balance;
- When a PSUR brings direct changes to the RMP for a medicinal product;
- At the request of the national competent authority, if applicable.

V.C.2.1 Types of the RMP documents to be submitted

The type of Risk Management Plan (RMP) that needs to be submitted to the national competent authority varies based on the type of drug product (innovator vs. generic) and its country of origin (European vs. non-European).

A. For Innovator Products – Table 3:

Marketing Authorization Holders (MAHs) for innovator products originating from European countries should submit the EU-RMP if it has been approved, along with the National Display RMP. If the EU-RMP is still pending approval, they should submit the CORE RMP.

For innovator products from non-European countries, the MAHs should submit the Global RMP, awaiting the EU-RMP approved version, along with the National Display RMPs.

B. For Generic Products – Table 3:

Marketing Authorization Holders (MAHs) for generic products originating from European countries should submit both the Abridged RMP, derived from the EU RMP, and the National Display RMP.

For generic products originating from non-European countries, the MAHs should submit both the Abridged RMP, derived from the Global RMP, and the National Display RMP.

C. For National MAH (Local Industry) – Table 3:

The National Industry is required to submit an Abridged RMP for locally manufactured generic products, derived from the innovator's RMP. For innovators or generics under licensed products, the National MAH must comply with the same requirements as those for innovator or generic products originating from European and non-European countries.

To note that, the Abridged RMP does not replace the National Display RMP. As for well-established older products, there is generally a facilitation process to avoid the submission of an RMP, but a justification is

needed, especially if the innovator does not have an RMP. Additionally, a National RMP display is requested in both cases.

Table 3. Submission of RMP per MAH Type

Product Type	A. Innovator Products		B. Generic Products		C. Local Industry	
Country of Origin	European Countries	Non-European Countries	European Countries	Non-European Countries	Locally Manufactured Generic Products	Innovator or Generic Under Licensed Products
RMP Type	EU-RMP (Integrated)	Core RMP awaiting EU-RMP approved version*	Abridged** RMP based on the EU RMP (Integrated)	Abridged** RMP based on the Global RMP	Abridged RMP based on the Innovator RMP	Same requirements as innovator or generic products from European and non-European countries
Submission of National Display RMP* **	Yes	Yes	Yes	Yes	Yes	Yes

Legend:
***CORE RMP/ Global RMP**: is a RMP prepared by the company in an acceptable format that contains all of the essential elements of the RMP*

****Abridged RMP:** An Abridged RMP for Generic drugs is a concise document with extracted information from the innovator-integrated RMP*

*** The National Display of the RMP is a country-specific summary of the global or EU RMP, adapted to show how risk management activities will be implemented in Lebanon.*

V.C.3. Requirements in specific situations

Generally, all parts of an RMP should be submitted. However, in certain circumstances, as detailed below, certain parts or modules may be omitted.

Table 4: Summary of minimum RMP requirements

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	✔								✔	✸	✸	✔	✸	✔

✸ Modified requirement

Please note that the naming and numbering of the RMP parts, modules & sections are standardized thus should NOT be changed or renumbered due to the omission of un-required sections.

V.C.4. Updates to the risk management plan

A RMP update should be submitted:

- At any time when there is a change in the list of the safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimization activities e.g. removing such activities from the RMP, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials.
- At the request of the national competent authority.

An update of the RMP might be considered when data submitted in the procedure results or is expected to result in changes of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities, or of routine risk minimization activities recommending specific clinical measures to address the risk. The need to update the plans to evaluate the effectiveness of risk minimization activities should also be considered with such updates.

Changes to the initial RMP should be tracked, and each submission should have a distinct version number and should be dated. A medicinal product can only have one “current” approved version of RMP. If several

updates to the RMP are submitted during the course of a procedure, the version considered as the "current" approved RMP for future updates and track-changes purposes should be the one submitted with the closing sequence of the procedure.

V.C.5. National Display of the RMP (country-specific) - for MAHs/MAAs having an EU RMP in place

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 minimization 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 need different or supplementary activities in the RMP for each region, although there will be core elements that 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 for a target population or indication.

Furthermore, individual countries may have different health systems, and medical practice may differ between countries, so the conditions and restrictions in the marketing authorization may be implemented in different ways depending upon national customs. MAH/MAAs are required to submit RMP to the national competent authority in Lebanon in the situations described in this Module section V.C.3.

Taking into consideration that the core elements of the product's RMP are common and for simplification, MAH/MAAs should always submit the National Display of the RMP, including its annexes, along with the required RMP document (see section V.C.2.1).

In these circumstances (submitting the National Display and the required RMP), the following conditions apply:

- When the referenced RMP (EU RMP, Abridged RMP, Global RMP, or Core RMP) is subject to update, the National Display of RMP should be updated in accordance.
- Minor differences may exist between this guidance and the RMP (EU RMP, Abridged RMP, Global RMP, or Core RMP). In this case, MAH/MAA may be asked by the national competent authority in Lebanon to submit additional information, use different tables, and/or provide clarification, etc.;

- The submitted RMP (EU RMP, Abridged RMP, Global RMP, or Core RMP) shall be the most updated version.
- The RMP (EU RMP, Abridged RMP, Global RMP, or Core RMP) shall be submitted with its annexes and reference materials.
- Generally, it is required that all the risk management activities applied globally/in the EU be applied in Lebanon as well, especially the risk minimization measures, including the measurement of their effectiveness. Accordingly, all activities, action plans and details especially the risk minimization ones (including the measurement of their effectiveness) stated in the submitted RMP (EU RMP, Abridged RMP, Global RMP, or Core RMP) - although unjustifiably skipped in the "National Display of the RMP"- are expected by default to apply to Lebanon and the MAH is required to adhere to them, EXCEPT otherwise clearly stated and justified by the MAH/MAA in the "National Display of the RMP" and agreed by the national competent authority.

The purpose of the "National Display of the RMP" is to:

- Highlight to what extent the risk management activities proposed to be implemented nationally adhere to the globally implemented plan;
- Provide justification for any differences when they exist (apart from what is implemented in the EU), including the needed national tailoring, if any;
- Include an assessment of whether there are any additional national/region-specific risks or not, describing what may be needed to manage those additional risks;
- Provide good evidence that the Local Safety Responsible (LSR)/Local QPPV or National QPPV has a clear understanding and commitment to the activities that will be implemented on the national level and how they will be implemented.

V.C.6. Template of the National Display of the RMP

A template of the National Display of the RMP is provided in a separate annex to Module V, and can be accessed from the ministry's webpage.

It is adapted from Annex II.3. of the Guideline on Good Pharmacovigilance Practices (GVP) for Arab Countries- Version 3 - https://who-umc.org/media/164038/the-good-pharmacovigilance-practice-for-arab-countries-v3-12-2015.pdf.