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I. PURPOSE

This Standard Operating Procedure (SOP) describes the procedure of the preparation, review, approval, submission of a Risk Management Plan (RMP) to Regulatory Authorities (RA) by PharmExpert LLC (Pharmex) in accordance with Good Pharmacovigilance Practices (GVP).

II. SCOPE

This procedure shall apply to staff of Pharmex involved in the processes of determining the submission rules, preparation, review, approval and submission of Marketing Authorization Holder's (MAH)'s RMP to whom Pharmex offer the service in line with the agreement.

III. RESPONSIBILITIES

Role	Responsibility
Senior Pharmacovigilance Specialist (SPVS)	• Preparation and submission of RMP
Head of Pharmacovigilance Department (HPVD)	• Review and approval of draft of RMP
MAH's QPPV (Qualified Person Responsible for Pharmacovigilance)	• Request the data from RA's database • Review and approval of final RMP
Quality Assurance Manager (QAM)	• Compliance monitoring

IV. DEFINITIONS

Abbreviations used in the text are spelled out on its first mention.

Risk management system (RMS) – a set of activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicines, including the assessment of the effectiveness of those activities and interventions.

For other terms and definitions refer to the SOP-QA-003 «Pharmacovigilance Glossary».

V. PROCEDURE

A. General specification

1. Aim of RMP

RMP is a detailed description of the RMS.

The aim of a RMP is to document the RMS considered necessary to identify, characterise and minimise the important risks of a medicinal product (MP).

RMP include information on:

- MP's safety profile;
- how its risks will be prevented or minimised in patients;
- plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine;
- measuring the effectiveness of risk-minimisation measures.

2. Overview of the RMP parts and modules

- Part I Product(s) overview
- Part II Safety specification
- Module SI Epidemiology of the indication(s) and target population(s)
- Module SII Non-clinical part of the safety specification
- Module SIII Clinical trial exposure
- Module SIV Populations not studied in clinical trials
- Module SV Post-authorisation experience
- Module SVI Additional EU requirements for the safety specification
- Module SVII Identified and potential risks
- Module SVIII Summary of the safety concerns
- Part III Pharmacovigilance plan (including post-authorisation safety studies)
- Part IV Plans for post-authorisation efficacy studies
- Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)
- Part VI Summary of the risk management plan
- Part VII Annexes

3. Submission Terms

RMPs are continually modified and updated throughout the lifetime of the MPs as new information becomes available. Companies need to submit an updated RMP,

MAHs must submit the RMP to RA as follows:

- To obtain a marketing authorization (MA) for a MP containing an active substance or a combination of active substances previously unapproved.
- To obtain primary MA or renewal of MA for a biological MP.
- Whenever the RMS is modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk-minimisation milestone being reached.
- When making significant changes to the existing MA, scope, aspects of production: new pharmaceutical form; new administration route; new method for the production of biotechnological drugs; introduction of pediatric indications; other significant changes in indications.

EU Risk Management Plan for <Invented name> (INN or common name)

RMP version to be assessed as part of this application:

RMP Version number: <Insert number>

An RMP should be assigned a new RMP version number and a date each time the RMP is updated and submitted for assessment (e.g. versions 0.1, 0.2, 0.3 etc. for an initial submission of an RMP; versions 1.1, 1.2, etc. and 2.1, 2.2 etc. for RMP updates post-authorisation).

The version number of the RMP version agreed at the time of the competent authority opinion should be the same as the one provided with the last eCTD submission in the procedure (most often with the closing sequence). It is advisable to use major version numbers for final approved RMP versions (e.g. version 1.0 at the end of the initial marketing authorisation application; 2.0, 3.0, etc. for post-authorisation updates).

Data lock point for this RMP: <Enter a date>

It is recommended that the Data Lock Point (DLP) should not be more than 6 months before the RMP sign-off date.

For initial marketing authorisation applications it usually reflects the DLP of the Clinical Safety Summary.

Date of final sign-off: <Enter a date>

The date of sign-off is the date when the draft RMP was considered finalised and ready for submission to the regulatory agency.

Rationale for submitting an updated RMP: <Not applicable for initial marketing authorisation application submission>

Summary of significant changes in this RMP: <Add high level description of major changes to each module>

<Other RMP versions under evaluation:>

This section is applicable for post-authorisation RMP updates when a different RMP version is still under assessment with another procedure.

If two or more parallel procedures contain RMP submissions, to facilitate assessment, it is usually advised to submit a common consolidated version of the RMP; the supporting Word version of the RMP included with the submission should include track changes (colour coded for each procedure), so that changes related to each procedure can be easily identified. This will also facilitate the finalisation of the RMP for each procedure.

Where the submission of a common, consolidated RMP version is not practical, distinct RMP documents may be submitted with each procedure (Word versions should also include tracked changes, per procedure). For further guidance please refer to European Medicines Agency post-authorisation procedural advice for users of the centralised procedure[1]. The best regulatory path for the RMP update

[1] available on EMA website http://www.ema.europa.eu

in case of multiple procedures potentially impacting on the RMP content should be discussed with the competent authority before submissions.

RMP Version number: <Insert number>

Submitted on: <Enter a date>

Procedure number: <indicate procedure number>,

<Details of the currently approved RMP:> *This section is not required for initial marketing authorisation applications.*

There can only be ONE currently approved RMP for a product(s).

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 shall be the one mentioned in the Opinion documents (most often same version is submitted with the closing sequence of the procedure).

Version number: <enter a version number>

Approved with procedure: <enter a procedure number>

Date of approval (opinion date): <dd/mm/yyyy>

QPPV name[2]:

The QPPV´s actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalised approved version of RMP.

In the case the option of oversight declaration has been selected and no signature has been submitted, the MAH should have the actual signature in their system, either in pen on paper, digital signature attached to the RMP document or any other electronic system of document management. For eCTD submission, this would be the RMP with the last eCTD sequence of the procedure (usually the closing sequence).

Select one of the options:

QPPV signature:

Or

QPPV oversight declaration: <The content of this RMP has been reviewed and approved by the marketing authorisation <holder´s> <applicant´s> QPPV. The electronic signature is available on file.>

[2] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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