

**CMD(h) GUIDANCEh RECOMMENDATION FOR MAHs MARKETING  
AUTHORISATION HOLDERS ON  
THE PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN  
IN THE MUTUAL RECOGNITION & AND DECENTRALISED PROCEDURES**

*November 2007*

*Doc. Ref.: CMDh/067/2007, Rev1  
July 2011*

## **1. INTRODUCTION (BACKGROUND)**

According to Article 8 (3)(ia) of Directive 2001/83/EC as amended the inclusion of “*a detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce*” is required when an application for a new marketing authorisation is made. A more detailed view on this is given in sections 2 and 3.

The requirements and format for the description of a pharmacovigilance system are covered in Volume 9A of *The Rules Governing Medicinal Products in the European Union*, Part 1, Chapter 2 ‘Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections’.

Pharmacovigilance obligations apply to all medicinal products authorised in the EU, whatever procedure was used for their authorisation, including products registered via Mutual Recognition Procedures (MRP) and Decentralised Procedures (DCP).

Guidance to marketing authorisation applicants (MAA) and marketing authorisation holders (MAH) on meeting the requirements for a detailed description of the risk management plan and the circumstances when it is appropriate to provide it, is provided in Part 1, Chapter 3 of Volume 9A of *The Rules Governing Medicinal Products in the European Union* (‘Requirements for Risk Management Systems’). This guidance is also applicable to products authorised through the centralised procedure and mutual recognition or decentralised procedures.

This CMD(h) guidance document aims to provide specific guidance for RMS and CMS on the submission of data related to Pharmacovigilance systems, the necessity for submission of Risk Management Plans (RMP) and on how the RMP is assessed during MRP and DCP. It should be read in conjunction with above mentioned documents.

## **2. SUBMISSION OF DESCRIPTION OF PHARMACOVIGILANCE SYSTEMS IN MRP/DCP DOSSIERS**

The requirements for submission of a detailed description of the pharmacovigilance system ([DDPS](#)) are the same for any marketing authorisation application, independently of the legal basis of the application or the procedure followed. These requirements are described in Volume 9A of *The Rules Governing Medicinal Products in the European Union*.

All applications require a description of their Pharmacovigilance system in section 1.8.1.

The RMS should follow this guidance in giving advice to companies.

### 3. SUBMISSION OF RMP IN MRP/DCP DOSSIERS

According to the 'Requirements for Risk Management Systems' as outlined in Volume 9A of *The Rules Governing Medicinal Products in the European Union* a detailed description of the risk management system should be submitted in the situations described below, in the form of an EU Risk Management Plan (EU-RMP):

- with the application for a new marketing authorisation for :
  - any product containing a new active substance
  - a similar biological medicinal product
  - a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product.
- with an application involving a significant change in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the Competent Authority that submission is not required.
- on request from a Competent Authority (both pre-and post- authorisation).
- at the initiative of a MAA/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorisation may require an EU-RMP:

- known active substances
- hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
- bibliographical applications
- fixed combination applications.

The risk management plan should be submitted according to the EU-template.

The requirements for an EU-RMP should be followed for applications submitted via the DCP and MRP.

For generic products submitted according to Article 10(1) of Directive 2001/83/EC as amended, an EU-RMP may not be required where it is considered that adequate knowledge and experience with the active substance and the known risk benefit profile of the product exist. However, an EU Risk Management Plan should be submitted with the application for a generic product, if there is a safety concern with the reference medicinal product, which has led to additional risk minimisation activities. Routine risk minimisation activities include use of the product information ([SPCSmPC](#), Package leaflet and labelling) to reduce the risk to patients. This includes the use of warnings and contraindications in the [SPCSmPC](#). Additional risk minimisation activities are those, which go beyond routine activities and include specific physician, pharmacist or patient educational material or patient alert cards etc. If, in future, new data become available that change the existing view of the safety of the active substance, an EU Risk Management Plan may then be considered necessary.

With regard to the submission of EU Risk Management Plans for hybrid applications (Art 10(3) of Directive 2001/83/EC as amended), the principles are the same as for generic applications according to Article 10(1) of Directive 2001/83/EC as amended. However, an EU Risk Management plan may also be needed for a hybrid medicinal product, even where there is no particular safety concern with

the reference medicinal product, if the changes compared with the reference medicinal product suggest that there may be different risks. An example could be if the indication differed for the reference medicinal product and suggested a different target population.

It is strongly recommended that discussions with the RMS on the need for and content of an RMP should take place in advance of submission and the RMS should follow this guidance in giving their advice to companies.

#### **4. ASSESSMENT OF DESCRIPTION OF PHARMACOVIGILANCE SYSTEMS AND RMP DURING THE MRP AND DCP**

##### *Responsibilities of RMS and CMS during validation*

A [detailed](#) description of the Pharmacovigilance system ([DDPS](#)) of the [applicant](#) should be included in Module 1.8.1 of the dossier.

[The application may also include more than one future MAH in addition to the applicant \(included in section 2.4.1 of the application form\), since additional MAHs could be applied for in each member state \(see “CMDh Guidance document for declaration form submission DDPS already approved by a competent authority \(CA\); CMDh website <http://www.hma.eu/91.html>”\).](#)

[The DDPS of any proposed future MAHs should also be submitted as part of the MRP/DCP application at day 0 of the procedure, together with the CMDh “Declaration form for the submission of DDPS already approved by a competent authority” \(see CMDh website: <http://www.hma.eu/91.html>\).](#)

[It is not possible to include future MAHs in the application form, which differ from the applicant, with a DDPS which has not been approved by a CA.](#)

If required (see above), the EU-RMP should be included in Module 1.8.2 of the dossier. If the submission of an EU-RMP is not required, the applicant should submit a justification in Module 1.8.2. The competent authorities should check the availability of

- the description of the Pharmacovigilance System, [\(s\), declaration form for the submission of DDPS already approved by a competent authority \(if applicable\)](#) and
- [an EU-RMP or the availability of a justification for not submitting an EU-RMP](#)
- [during validation. At this stage this is only an administrative check.](#)

##### *Responsibilities of RMS and CMS during the MRP or DCP*

The RMS should include an assessment of the [applicant’s](#) description of the Pharmacovigilance System in the Overview part of the Assessment Report (AR), [unless this DDPS has already been assessed and approved by another CA.](#)

[The RMS should include an overview of any DDPSs submitted for any future MAHs together with the confirmation that these DDPSs have already been assessed as stated in the respective Declaration forms....](#)

If an EU-RMP is not submitted, the RMS should include an assessment of the justification in the Overview part of the Assessment Report (AR).

If an EU-RMP is part of the submission, this document should be assessed by the RMS. Part 1, Chapter 3 of Volume 9A of *The Rules Governing Medicinal Products in the European Union* requires submission of a Safety Specification, a Pharmacovigilance Plan, and Evaluation of the need for risk minimisation activities and, where specific measures to limit risk are needed, a Risk Minimisation Plan. An assessment of all elements of the EU-RMP should be included in Module 5 of the AR (Clinical Part) following the agreed template, together with a summary in the Overview section.

To achieve this, an expert in pharmacovigilance should be part of the assessment team in the RMS.

[CMD\(h\) Guidance for MAHs on](#)

[the pharmacovigilance system and risk management plan](#)

[in the mutual recognition & decentralised procedures](#)

[on the Pharmacovigilance System and Risk Management Plan](#)

[in the Mutual Recognition and Decentralised Procedures](#)

[November 2007](#) Page CMDh Recommendation for Marketing Authorisation Holders

CMDh/067/2007, Rev1, July 2011

Page 3/7

In principle, CMS should rely on the assessment of the RMS, but comments on the EU-RMP may be circulated according to the usual agreed procedures. Comments of the CMS on the EU-RMP should be dealt with during the procedure, and there should be agreement on the description of the Pharmacovigilance System and the EU-RMP before finalisation of the MRP/DCP. The AR on the RMP should be detailed enough to give the CMS a good overview.

#### *Handling of updates to the description of Pharmacovigilance Systems*

Guidance on the submission of updates to the information provided in the description of the Pharmacovigilance System is given in part I, section 2.2.1 of Volume 9A of the *Rules Governing Medicinal Products in the European Union*. Updates should be made [as via appropriate variation applications \(type IA, type IB or type II variations\)](#).

#### *Handling of updated EU-RMP*

The RMS is responsible for checking compliance with the agreed actions and milestones. Guidance on the submission of an updated EU-RMP is given in Part I, section 3.14 of Volume 9A of the *Rules Governing Medicinal Products in the European Union*. An updated EU-RMP should be submitted at the same time as the next Periodic Safety Updated Report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation. In addition an updated EU-RMP should be submitted:

- 1) when new information is received that may impact on the current safety specification, pharmacovigilance plan or risk minimisation activities
- 2) within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached or the results of a study becoming available
- 3) at request of the Competent Authority.

If an updated EU-RMP is submitted in a separate submission (i.e. not at the same time as a PSUR), or outside a variation procedure ~~number e.g. to add a new indication), the appropriate variation application should be assigned for each follow up submission (CC/D/nnnn/sss/FU/vvv). Agreement on the conclusions should be reached in principle according to a timetable for submitted.~~

Ad 1) a type II variation ~~application is required (classification C.I.z) in case this has a significant impact on safety.~~

Ad 2) the results of the study should be submitted via a type II variation application (classification C.I.z or C.I.4 in case the results lead to changes to the SmPC). The updated RMP can be submitted as part of the same single type II variation application.

Ad 3) the choice of the type of variation application will depend on the reason for requesting the updated RMP. In cases where the change is considered to have a significant impact on the safety of the product, a type II variation application (classification C.I.z) should be submitted.

[The inclusion of a new RMP in a dossier should be submitted as a type II variation application \(classification C.I.z\).](#)

#### *Changes to previously agreed EU-RMP*

Changes to EU-RMPs to incorporate information due to fulfilment of previously agreed activities will not generally require a type II variation. However, the revised EU-RMP should be submitted ~~at when~~ the next important milestone is reached. Otherwise the revised EU-RMP should be submitted as a type IB variation application.

A Type II variation is required if the MAH wishes to make changes to previously agreed risk minimisation activities (e.g. [SPCSmPC](#) or other product specific risk minimisation measures) within

the EU-RMP. In agreement with the RMS a 30 day expedited timeframe may be followed. In the case that changes to the [SPCSmPC](#) are proposed, only one type II variation is required.

In situations where the MAH wishes to substantially change the agreed milestones in the EU-RMP (e.g. the MAH wishes not to perform, or wishes to make a major amendment to, a study which was agreed in a RMP), a type II variation is required.

[Changes to already approved educational materials may be submitted as a type IB variation application.](#)

#### *Involvement of PhVWP*

In principle, involvement of the PhVWP should be initiated by the RMS, however, a CMS may also ask for input from the PhVWP via the RMS.

Assessment of the EU-RMP and discussion between Member States on this issue is part of the MRP/DCP. Where additional pharmacovigilance measures are proposed input from the PhVWP should be considered. For procedural aspects on involvement of the PhVWP, see the Guidance document on communication between PhVWP and CMD(h) and the guidance on the handling of Risk Management plans by PhVWP.

Timing the involvement of the PhVWP during the procedure may be difficult, especially during the MRP and therefore, the need for involvement of PhVWP should be carefully considered.

In MRP, the PhVWP should preferably become involved around day 50 of the procedure. In DCP, the PhVWP should preferably become involved during Assessment Step 2. Input should be sought as soon as possible to ensure that dates of the meetings are met within the timetables of the procedures.

Input of PhVWP during the assessment of follow-up submissions of EU-RMP is possible and timing should be announced by the RMS.

#### **Abbreviations used:**

CMD(h) – Co-ordination group on Mutual recognition and Decentralised procedure (human)

CMS – Concerned Member State

CTS – Communication and Tracking System for the mutual recognition procedure

DCP – Decentralised Procedure

MRP – Mutual Recognition Procedure

MAA – Marketing Authorisation Applicant

MAH – Marketing Authorisation Holder

NtA – Notice to Applicants

PhVWP – Pharmacovigilance Working Party

RMP – Risk Management Plan

RMS – Reference Member State

[SPCSmPC](#) – Summary of Products Characteristics

[DDPS](#) – Detailed Description of the Pharmacovigilance System

#### **Related documents:**

The Rules Governing Medicinal Products in the European Union, Volume 9A, February 2007

## ANNEX

### **GUIDANCE ON HANDLING OF RISK MANAGEMENT PLANS FOR MRP AND DCP AUTHORISED PRODUCTS BY THE PHARMACOVIGILANCE WORKING PARTY**

#### **Purpose**

The purpose of this guidance is to define a practical procedure to ensure timely handling of complex risk management plans and effective contribution to their assessment by all PhVWP members.

#### **Responsibilities**

It is the responsibility of the PhVWP Chairperson and Secretariat to ensure that this procedure is adhered to within the PhVWP.

#### **Procedure**

- a) MR/DC-RMPs where additional pharmacovigilance measures are proposed, and where involvement of PhVWP is considered necessary or other reasons for PhVWP assessment not previously assessed by the PhVWP.

<b>Step</b>	<b>Action</b>	<b>Responsibility</b>	<b>Day</b>
1.	Submitted RMPs (both pre-authorisation and post-authorisation) are screened and assessed by the RMS.	RMS	32 days before a PhVWP report is required
1.1	A notification for discussion on specific issues arising from the submitted RMP is prepared and submitted to the PhVWP Secretariat, along with a proposed timetable for discussion at the PhVWP Plenary meeting.	RMS	32 days before a PhVWP report is required
1.2	A proposal for allocation of one or more PhVWP co-opted member is sent to the PhVWP Secretariat, to the Chairperson and to the Lead PhVWP Member of the MS that has the Rapporteurship on the product.	RMS	32 days before a PhVWP report is required
1.3	The eligibility of the proposed PhVWP co-opted member is confirmed and the allocation of RMPs is tracked in a log.	PhVWP Chairperson/ Secretariat	32 days before a PhVWP report is required
1.4	An assessment report is prepared in conjunction with the PhVWP Co-opted Member(s) and is circulated to the PhVWP Members for comments	Lead PhVWP Member	16 days before a PhVWP report is required
1.5	A draft “PhVWP Report on the assessed RMP” is prepared and circulated to the RMS.	Lead PhVWP Member	2 days before a PhVWP report is required
1.6	A PhVWP sub-group on RMPs is held on the margins of the PhVWP plenary meeting.	Chairperson/ PhVWP Secretariat/ All involved PhVWP Members	Around the day a PhVWP report is required
1.7	The assessed RMP is discussed in the plenary.	PhVWP Plenary	Around the day a PhVWP report is required
1.8	The “PhVWP Report on the assessed RMP” is updated with the outcome of the plenary discussion, and agreed by the PhVWP.	PhVWP Plenary	Around the day a PhVWP report is required

Step	Action	Responsibility	Day
			required
1.9	The “PhVWP Report on the assessed RMP” is sent to the CMD(h) for adoption	PhVWP Secretariat/PTL	At the latest the day a PhVWP report is required

b) MR/DC-RMPs previously assessed by the PhVWP, and where involvement of PhVWP is again considered necessary:

Step	Action	Responsibility	Day
2.	When necessary, the review of implementation of the RMP is requested for scheduling on the agenda of the PhVWP meeting.	Lead PhVWP Member/ PhVWP Secretariat	32 days before a PhVWP report is required
2.1	An assessment report on the status of implementation of the RMP is prepared in conjunction with the PhVWP Co-opted Member(s) assigned to the RMP and is circulated to the PhVWP Members for comments	Lead PhVWP Member	16 days before a PhVWP report is required
2.2	A draft “PhVWP Report on the assessed RMP” is prepared and circulated to the PhVWP Members.	Lead PhVWP Member	Around the day a PhVWP report is required
2.3	The status of implementation of the RMP is discussed in the plenary meeting.	PhVWP Plenary	Around the day a PhVWP report is required
2.4	The “PhVWP Report on the assessed RMP” is updated with the outcome of the plenary discussion, and agreed by the PhVWP.	PhVWP Plenary	Around the day a PhVWP report is required
2.5	The “PhVWP Report on the assessed RMP” is sent to the RMS for adoption	PhVWP Secretariat/PTL	At the latest the day a PhVWP report is required

## Records

The PhVWP Secretariat will maintain a log in order to track the allocation of PhVWP co-opted members to RMPs. This would ensure feasible distribution of workload and would help with the selection of the most appropriate expertise for the required topic.

The PhVWP Report on the assessed EU-RMP should always include, in its “Follow-up” section, detailed description of the RMP milestones, that will serve as a basis for future review of the implementation of the RMP.

A tracking system for these milestones is to be developed. As an interim measure the PhVWP Secretariat will keep track of these milestones (and of any amendment to these) for the scheduling of the review of the EU-RMP implementation at the PhVWP meetings.