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*This Q&A was developed in 2012 to provide practical guidance concerning the initial phases of operation of the pharmacovigilance legislation and will not be further updated. Please note that some questions are no longer relevant or, otherwise, have been integrated in the EMA post-authorisation guidance.*

## Questions and Answers to support the implementation of the Pharmacovigilance legislation - UPDATE, NOVEMBER 2012

### Introduction

This Question and Answer (Q&A) document provides practical considerations concerning the initial phases of operation of the new pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU). The Q&A applies to all medicinal products for human use regardless of the route of authorisation. Any specificities depending on the route of authorisation (i.e. centralised procedure versus mutual recognition/decentralised procedure and purely national procedure) are highlighted when appropriate.

The Q&A document should be read in conjunction with Commission Questions and Answers on transitional arrangements. The questions and answers in this document represent the view of the EMA and Member States and have been subject to consultation with the European Commission. In case of doubt reference is given to the above-mentioned Union Directive and Regulation as well as to the Commission Implementing Regulation (EU) No 520/2012.

This document provides a series of questions and answers to clarify procedural elements in relation to the implementation of the new legislation. The questions are organised into the following themes:

- Good Pharmacovigilance Practices (GVP) guidelines
- Pharmacovigilance system master file (PSMF) and summary of the pharmacovigilance system
- Risk Management Plan (RMP)

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- Non-interventional Post-authorisation safety studies (PASS)
- Periodic Safety Update Reports (PSUR) and EURD list
- Literature monitoring
- Product information and black symbol
- Adverse Drug Reaction (ADR) reporting and signal management
- Renewals

The Regulation and Directive as referred to above entered into force respectively on 2 July and 21 July 2012. Therefore when referring to dates of application for both centrally authorised products (CAPs) and nationally authorised products (NAPs) including products authorised through the mutual recognition and decentralised procedures (MRP/DCP), the Q&A states 2 / 21 July 2012.

This document is intended to be updated with additional clarifications as the implementation of the new pharmacovigilance legislation progresses.

For further questions on the implementation of the new pharmacovigilance legislation that you would consider useful to add to this Q&A, please email the following mailbox [QandA-PV-legislation@ema.europa.eu](mailto:QandA-PV-legislation@ema.europa.eu). Please note that no individual responses will be provided but questions received will be reviewed on a regular basis and form the basis for any further questions and answers updates. This is without prejudice to any formal request for information or documents that stakeholders may make to the EMA.

For queries in relation to a specific centrally authorised product, applicants/MAHs are advised to raise these with their Product Team Leader.

For queries in relation to a specific medicinal product authorised through the MRP/DCP, applicants/MAHs are advised to liaise with the Reference Member State. For purely nationally authorised medicinal products, the applicants/MAHs are advised to contact the relevant national competent authority.

Please find at the end of this document a list of abbreviations used throughout this document.

Where the Q&As have been updated since the last version, this is clearly indicated.

## **1. Good Pharmacovigilance Practices (GVP) guideline**

### ***1.1. Where can I find information on Good Pharmacovigilance Practices (GVP)?***

In order to support the implementation of the new legislation for pharmacovigilance, a new set of guidelines for the conduct of pharmacovigilance in the EU is under development which will replace the current set in Volume 9A of the Rules Governing Medicinal Products in the EU.

For more information on the GVP, please refer to the GVP information on the [EMA Website](#).

### ***1.2. Will the Volume 9A remain applicable after July 2012? (Update July 2012)***

With the application of the new pharmacovigilance legislation in July 2012, Volume 9A is superseded by the guidance on Good Pharmacovigilance Practices (GVP). However, GVP will indicate where there is

a transition period for the implementation of the new requirements and/or where the GVP modules are not yet available. Volume 9A remains the reference as applicable until the transition period ends or until that specific GVP modules are published as final. Final GVP modules can be found on the [EMA website](#).

## **2. Pharmacovigilance system master file (PSMF) and summary of the pharmacovigilance system**

### ***2.1. When am I required to introduce the pharmacovigilance system summary in my marketing authorisation?***

After 2 July 2012 (for CAPs) and 21 July 2012 (for NAPs), applicants/MAHs are required to include a summary of the applicant/MAH's pharmacovigilance system:

- At the time of submission of an initial marketing authorisation application.
- For existing marketing authorisations (MAs), in the following cases whichever is the earlier :
  - i. At the time of submission of the renewal application,
  - ii. At time of submission of the annual renewal application for a conditional marketing authorisation through the centralised procedure,
  - iii. by 2 (for CAPs) / 21 (for NAPs) July 2015.

These requirements apply to all existing MAs with or without a detailed description of the pharmacovigilance system (DDPS) in their dossier.

In accordance to the Commission Questions and Answers on transitional arrangements, for pending initial marketing authorisation applications and renewal applications on 2 / 21 July 2012, there is no obligation to replace the Detailed Description of the Pharmacovigilance System (DDPS) by the summary of the pharmacovigilance system during the course of the evaluation procedure. In such circumstances, on a voluntary basis, the applicant may supplement their application during evaluation under certain conditions (please refer to question 2.2). If the application is not upgraded during evaluation, the same rules as for existing MAs apply (please refer to question 2.2).

The PSMF is not part of the MA dossier. It should be kept up-to-date and permanently available for inspection and should be provided within 7 days to the competent authorities if requested.

### ***2.2. Can I introduce the PSMF earlier than the mandatory deadlines? (Update November 2012)***

- **For pending initial marketing authorisation and renewal applications (MAAs) submitted before 2 / 21 July 2012 but finalised after that date**

On their own initiative, applicants/MAHs may replace after 2 / 21 July 2012 in their pending application the detailed description of the pharmacovigilance system by the new summary of the pharmacovigilance system provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP Module II.

For practical reasons for CAPs, if applicants/MAHs want to supplement their applications, the EMA strongly recommends the following time points to submit the pharmacovigilance system summary :

- For pending initial marketing authorisation applications,
  - at the time of the day 121 responses to list of questions or at the latest by day 181 (responses to the list of outstanding issues) of the procedure.
- For pending renewal applications,
  - at the time of the responses to the list of questions (if any) time permitting and upon agreement with the EMA.

If the Committee for Medicinal Products for Human Use (CHMP) has raised some concerns on the DDPS/pharmacovigilance system during the procedure, the applicant/MAH should address all questions raised in writing in their response document in order to address the outstanding concerns even if they introduce the summary of the pharmacovigilance system.

For NAPs including MRP/DCP products, introduction of the pharmacovigilance system summary during the course of the procedure should be agreed upon with the Reference Member State for mutual recognition and decentralised procedures or the national competent authority concerned for purely nationally authorised products / applications.

- **For existing marketing authorisations granted before 2 / 21 July 2012 and pending applications at the time of implementation that have not been upgraded during evaluation**

On a voluntary basis, marketing authorisation holders (MAH) may introduce a summary of the pharmacovigilance system at an earlier stage in the period between 2 / 21 July 2012 and 2 / 21 July 2015 provided that the PSMF fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP Module II (please refer to questions 2.3 and 2.4).

This also applies to marketing authorisations granted after 2 / 21 July 2012 but for which the applications were submitted before the application of the new legislation and which were not upgraded to the new requirements during the evaluation.

### ***2.3. How can I introduce the PSMF and the pharmacovigilance system summary in advance of the mandatory deadlines? (Update November 2012)***

In order to introduce, on a voluntary basis, the summary of the pharmacovigilance system to an existing marketing authorisation, the marketing authorisation holder should be able to fully comply with the new legal requirements for the PSMF as set out in the Commission Implementing Regulation and as detailed in the GVP Module II. For the purpose of updating the dossier the MAH would be required to provide in Module 1.8.1 of the dossier the pharmacovigilance system summary including the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person

- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC,
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

The applicant/MAH may combine this information in one single statement, signed by the applicant/MAH and QPPV. Irrespective of whether combined or not, the statement should refer to the required wording as per Article 8(3)(ia) of Directive 2001/83/EC “the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC”.

If available, the PSMF number assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement (see question 2.14). Applicants/MAH are encouraged to request a PSMF number (MFL EVCODE) for their PSMF in advance of the relevant application introducing the PSMF (marketing authorisation, renewal or variation applications) in order to include the PSMF number in their application under Module 1.8.1; however this information is not part of the compulsory elements as per Article 8(3)(ia) of Directive 2001/83/EC.

For further information on the PSMF number (MFL EVCODE) please see question 2.14 of this document.

In order to introduce the pharmacovigilance system summary in the marketing authorisation, the MAH should submit a variation. The classification of the variation will be defined in the revised variation classification guideline. Pending the publication of the revised variation classification guideline, the type of variation has been defined through an Article 5 procedure in accordance with Regulation (EC) No 1234/2008. For more information, please see question 2.4.

***2.4. As the revised variation classification guideline is not yet available, what type of variation should I submit to include the pharmacovigilance system summary? (Update November 2012)***

Pending the publication of the final revised variation classification guideline, the CMDh issued a recommendation on classification of two unforeseen variations in accordance with Article 5 of Regulation (EC) No 1234/2008 one for the introduction of the pharmacovigilance system summary and the other for changes to the QPPV names and contact details and to the PSMF location which can be found on the [CMDh website](#). These are classified as type IA<sub>IN</sub> variation and are applicable to both centrally authorised products and products authorised through the mutual and decentralised procedures.

Changes to the QPPV information can be introduced as part of the first introduction of the pharmacovigilance system summary in one single variation type IA<sub>IN</sub>, as the QPPV information is part of the required information in the summary. If the QPPV information is changed as part of the introduction of the summary of the pharmacovigilance system, the MAH should clearly indicate the change in the application form (i.e. in the present/proposed table of the application form).

The transition period to introduce, voluntarily, the summary of the pharmacovigilance system applies per marketing authorisation (outside of the mandatory introduction at time of renewal), therefore it is up to the MAH to decide whether to introduce the summary of pharmacovigilance system for each product at different times or to introduce the summary for several products at the same time. Once a product is included in a PSMF, the relevant type IA<sub>IN</sub> should be submitted to update the MA for that product and to reflect the switch to the PSMF for the product concerned.

## **2.5. Can I submit a 'one-off' grouped variation to introduce the pharmacovigilance system summary for all my medicinal products across all the Members States? (Update November 2012)**

Article 7.2(a) of Regulation (EC) No 1234/2008 sets out the possibility for a marketing authorisation holder to group several Type IA/IA<sub>IN</sub> variations under a single notification to the same relevant authority. For instance one Type IA or IA<sub>IN</sub> affecting several medicinal products can be grouped for the same MAH. Please see EMA post-authorisation procedural advice – [Grouping of variations](#).

The same grouped variation may be used to introduce a summary of the pharmacovigilance system for several medicinal products with or without a DDPS. In that case, the information on which product has a DDPS and which product does not should clearly appear in the application form (i.e. in the present/proposed table of the application form).

Therefore, the same MAH can submit a grouped Type IA<sub>IN</sub> variation which only includes those medicinal products authorised through the centralised procedure in order to introduce the pharmacovigilance system summary at the same time for all the relevant CAPs. The concept of worksharing does not apply to type IA/IA<sub>IN</sub> variations. Therefore the same variation affecting also nationally authorised medicinal products will need to be submitted independently to the competent authorities of each Member State and can also be grouped per Member States. However, there are possible arrangements for grouping of type IA/IA<sub>IN</sub> variations in the mutual recognition procedure which are detailed in the [Best Practice Guides](#) for the submission and processing of variations in the mutual recognition procedure.

## **2.6. My marketing authorisation does not contain a DDPS, do I have to maintain a PSMF and submit a summary of the pharmacovigilance system?**

As set out in the Commission Questions and Answers on transitional arrangements, the obligation to maintain a PSMF applies to all existing marketing authorisations irrespective of whether they contain a DDPS or not. As a consequence, a summary of the pharmacovigilance system needs to be submitted at the time of the renewal or through the appropriate variation not later than 2 / 21 July 2015.

## **2.7. Where should I provide the summary of the pharmacovigilance system in my marketing authorisation/ renewal / variation application? (Update November 2012)**

The following information should be provided as part of the summary of the pharmacovigilance system in Module 1.8.1 of the dossier:

- proof that the applicant/MAH has at his disposal a qualified person responsible for pharmacovigilance
- the Member State in which the qualified person resides and carries out his/her tasks
- the contact details of the qualified person
- a statement signed by the applicant/MAH to the effect that the applicant/MAH has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC
- a reference to the location where the PSMF for the medicinal product is kept.

The applicant/MAH may combine this information in one single statement, signed by the applicant/MAH and by the QQPV.



Irrespective of whether combined or not, the statement should refer to the required wording as per Article 8(3)(ia) of Directive 2001/83/EC “the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC”.

If available, the PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPPD) should be included in the statement (see question 2.14). Applicants/MAH are encouraged to request a PSMF number for their PSMF in advance of the relevant application introducing the PSMF (marketing authorisation, renewal or variation applications) in order to include the PSMF number in their application, in Module 1.8.1; however this information is not part of the compulsory elements as per Article 8(3)(ia) of Directive 2001/3/EC. For further information on how to apply for the PSMF number (MFL EVCODE) please see question 2.14 of this document.

### ***2.8. Can I introduce the summary of the pharmacovigilance system within the annual renewal application for my conditional marketing authorisation in the centralised procedure?***

The summary of the pharmacovigilance system should be submitted as part of the annual renewal application for a conditional marketing authorised through the centralised procedure in accordance with Article 14(7) of Regulation (EC) 726/2004.

### ***2.9. Can I introduce the summary of the pharmacovigilance system within my extension application in accordance with the Annex I of Regulation (EC) No 1234/2008? (Update July 2012)***

The summary of the pharmacovigilance system is generally expected to be submitted as a grouped variation with the extension application. For Mutual Recognition/Decentralised procedures, where the extension will lead to a new marketing authorisation, the summary of the pharmacovigilance system can be included in the extension application.

### ***2.10. What information will be made public on the EU web-portal regarding pharmacovigilance contact details and PSMF locations? Will details of the QPPV be made public?***

Article 26(1)(e) of the Regulation (EC) No 726/2004 places a responsibility on the EMA, in collaboration with Member States, to make public, at least, a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products for human use authorised in the Union. On this basis:

➤ Pharmacovigilance enquiries

EMA will publish contact information for pharmacovigilance enquiries from the data submitted under Article 57(2) of the Regulation (EC) No 726/2004, as follows:

- email address for pharmacovigilance enquiries (Art 57(2) data field AP.7 enquiryemail)
- phone number for pharmacovigilance enquiries (Art 57(2) data field AP.8 enquiryphone)

➤ Location of PSMF

EMA will publish the locations in the Union where pharmacovigilance system master files are kept, from the data submitted under Article 57(2) of the Regulation (EC) No 726/2004, as follows:

- Code assigned to the PSMF (Art 57(2) data field MF.2 ev\_code)

- Company name (Art 57(2) data field MF.3 mflcompany)
- PSMF location country code (Art 57(2) data field MF.10 mflcountrycode)

No information on the QPPV will be published by the EMA unless it is the same as that listed above (Art 57(2) XEVMPD data fields AP.7, AP.8, MF.2, MF.3, or, MF.10).

### **2.11. Which changes to the pharmacovigilance system summary require a variation? (Update November 2012)**

The initial introduction of the pharmacovigilance system summary requires the submission of a variation (please refer to question 2.3).

From those elements included in the pharmacovigilance system summary, changes to the QPPV and/or QPPV contact details and/or to the PSMF location will require the submission of a variation application. Pending the publication of the final revised variation classification guideline, the CMDh issued a recommendation on classification of an unforeseen variation in accordance with Article 5 of Regulation (EC) No 1234/2008 for changes to the QPPV names and contact details and to the PSMF location which can be found on the [CMDh website](#). This is classified as type IA<sub>in</sub> variations and is applicable to both centrally authorised products and products authorised through the mutual and decentralised procedures.

### **2.12. Do I need to have a PSMF in place and to submit a pharmacovigilance system summary for my herbal medicinal product?**

The requirement to operate a pharmacovigilance system and to maintain and make available on request a pharmacovigilance system master file also applies to traditional herbal medicinal products. However, the requirement to submit a summary of the pharmacovigilance system does not apply to the traditional-use registration. By analogy to the transitional period for the medicinal products, the PSMF for traditional herbal medicinal products should be in place not later than 21 July 2015.

For other herbal medicinal products not falling within the scope of the traditional-use registration, the requirement to operate a pharmacovigilance system applies and a summary of the pharmacovigilance system will be required for any initial marketing authorisation application after 2 / 21 July 2012, or for existing marketing authorisations at the time of renewal or by 2 / 21 July 2015 at the latest (please refer to questions 2.1 and 2.2).

### **2.13. Do I need to have a PSMF in place and to submit a pharmacovigilance system summary for my homeopathic medicinal product?**

The requirements to operate a pharmacovigilance system, to maintain and make available on request a pharmacovigilance system master file and to submit a summary of the pharmacovigilance system do not apply to the homeopathic medicinal products registered via the simplified registration procedure.

For other homeopathic medicinal products not falling within the scope of the simplified registration, the requirement to operate a pharmacovigilance system applies and a summary of the pharmacovigilance system will be required for any initial marketing authorisation application after 2 / 21 July 2012, or for existing marketing authorisations at the time of renewal or by 2 / 21 July 2015 at the latest (please refer to questions 2.1 and 2.2).



## **2.14. How can applicants/MAHs acquire a PSMF number for their PSMF? (Update November 2012)**

The PSMF number is a unique code (MFL EVCODE) assigned by the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) system to a specific master file and master file location.

Applicants/MAH are encouraged to request a PSMF number for their PSMF in advance of the relevant application introducing the PSMF (marketing authorisation, renewal or variation applications) in order to include the PSMF number in their application, in Module 1.8.1. However this information is not part of the compulsory elements for the summary of the pharmacovigilance system as per Article 8(3)(ia) of Directive 2001/83/EC.

In order to apply for a PSMF number, applicants/MAH will need to be registered with EudraVigilance. Information on how to register with the EudraVigilance system and initiate the electronic submission of information on authorised medicinal products are available through the [Eudravigilance webpage](#).

Following registration with Eudravigilance, the applicant/MAH should submit electronically in the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) the pharmacovigilance system master file location information using the agreed eXtended EudraVigilance Medicinal Product Report Message (XEVPRM) format as referred to in chapter IV, Article 26, paragraph 1(a) of the Commission Implementing Regulation. A unique code (MFL EVCODE) for the master file location will be assigned when the XEVPRM is processed in the XEVMPD. The assigned MFL EVCODE will be provided to the applicant/MAH as part of the XEVPRM Acknowledgement message for the MFL EVCODE request.

For further information as how to apply for the MFL EVCODE, please refer to the [Detailed Guidance on electronic submission of information on medicines](#).

Further guidance on how to maintain information on the PSMF location as part of the electronic submission of information on medicinal products in accordance with Article 57(2), second subparagraph of Regulation (EC) no 726/2004 will be published by the EMA.

This is also explained in GVP Module II on Pharmacovigilance system master file.

Note: In cases where a MAH hosts two different PSMFs at the same location, the MAH should obtain two separate EVCODEs from the XEVMPD that relate to two different PSMF location entries. These two PSMF locations will be identical but the comment field within the PSMF location of the XEVMPD should be used by the MAH to include an internal MAH reference to distinguish which PSMF is related the specific PSMF Location EVCODE (MFL EVCODE).

Any technical queries including questions on maintenance, should be sent to [Eudravigilance@ema.europa.eu](mailto:Eudravigilance@ema.europa.eu).

## **2.15. Is there a PSMF template following the new pharmacovigilance legislation? (New July 2012)**

There is no specific “PSMF template” developed. The structure and content of the PSMF as well as its maintenance is defined by the Commission Implementing Regulation and in the GVP Module II.

**2.16. Pharmacovigilance Master File location: can the server of the Pharmacovigilance System Master File be physically located and administered outside EU if it is validated and operational/accessible 24/7 for EU markets and EU QPPV? (New July 2012)**

According to the Article 5(3) of Commission Implementing Regulation, the pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time and a clearly arranged printed copy can be made available for audits and inspections.

In addition, Article 7 of the Commission Implementing Regulation clarifies that:

1. The pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates.
2. The marketing authorisation holder shall ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.
3. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.
4. Whenever the pharmacovigilance system master file is kept in electronic form in accordance with Article 5(3), it is sufficient for the purposes of this Article that the data stored in electronic form is directly available at the site where the pharmacovigilance system master file is kept.

**2.17. Can I introduce a new DDPS to my MA authorised before 2 / 21 July 2012 with no DDPS? (New November 2012)**

Under the new legislation, it is not possible to introduce a DDPS for an “old” MA with no DDPS. In order to introduce new elements to a MA, the new elements should be in accordance to the current legislation which only refers to the summary of the applicant/MAH's pharmacovigilance system as per Article 8(3)(ia) of Directive 2001/83/EC.

If a MAH wants to introduce a pharmacovigilance system in their MA they should submit the relevant variation to introduce the summary of their pharmacovigilance system.

**2.18. Do I need to keep my DDPS up-to-date after 2 / 21 July 2012? (New November 2012)**

The MAH has the obligation to keep their MAs up-to-date, including the DDPS. As long as a DDPS is maintained in the MA (i.e. before the introduction of the summary of the pharmacovigilance system), the obligation to submit the relevant variations to update the DDPS continues to apply. The transition provisions to introduce the summary of the Pharmacovigilance system (at the time of renewal or at the latest by 2/21 July 2015) do not waive the obligation to keep the DDPS up-to-date until the summary of the pharmacovigilance system is introduced.

**2.19. Can I introduce a different DDPS following a transfer of the MA? (New November 2012)**

Considering the deadlines for the transitional period set out in the legislation, a transfer of a MA does not trigger the requirement to switch to the summary of the pharmacovigilance system.

If as a consequence of the transfer of the MA, the pharmacovigilance system is changed, the MAH has the obligation to include the relevant description or summary of the pharmacovigilance system.

For MAs without a DDPS, if the MAH is considering introducing a pharmacovigilance system, it is only possible to introduce the summary of the pharmacovigilance system (see question 2.17).

For MAs with a DDPS, following a transfer a different DDPS can be introduced through the appropriate variation, regardless if this new DDPS has or has not been previously assessed.

According to the current variation classification, the classification C.I.8 should be used *“Introduction of a new Pharmacovigilance system”*.

## **2.20. When does the PSMF need to be in place for initial MA application? (New November 2012)**

As per GVP Module II – Pharmacovigilance system master file, section II.C.1.1. “Applicants are required, at the time of initial marketing authorisation application, to have in place a description of the pharmacovigilance system that records the system that will be in place and functioning at the time of grant of the marketing authorisation and placing of the product on the market. During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.

[...]

The pharmacovigilance system master file shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.”

The PSMF should be available during evaluation as it may be requested.

The pharmacovigilance system will have to be in place and functioning at the time of grant of the marketing authorisation and placing of the product on the market.

For more guidance on the requirements for pharmacovigilance system and PSMF, please refer to the relevant Good Pharmacovigilance Modules.

## **3. Risk Management Plan (RMP)**

### **3.1. Am I required to have a risk management plan for my initial marketing authorisation application?**

All applicants submitting an initial MAA after 2 / 21 July 2012 irrespective of the legal basis of their MA application are required to submit an RMP (please see questions 3.7 and 3.8).. This includes generic MA applications.

For pending initial marketing authorisation applications on 2 / 21 July 2012 which do not contain an RMP, there is no obligation to submit an RMP during the course of the evaluation procedure.

### **3.2. Do I have to continue to operate the RMP for my existing medicinal product?**

For those MAs granted before 2 / 21 July 2012 with an existing RMP, the MAH should continue to operate and update the risk management plan as detailed in the GVP Module V.

### **3.3. For my risk management plan to be submitted shortly after 2 / 21 July 2012, what format should I use? (Update November 2012)**

As set out in the Commission Implementing Regulation, the new format and content for RMPs shall apply from 10 January 2013 to new or updated RMP submitted as of that date. The template for the RMP has been updated and can be found on the [EMA website](#).

During the transitional period, applicants and marketing authorisation holders can either use the old or new format for a new RMP or an update of the RMP. If there are conditions and study types as referred to in Article 21a, 22 and 22a of Directive 2001/83/EC or in Article 9(4), 10a, 14(7) and 14(8) of Regulation (EC) No 726/2004 these should also be included in the RMP whichever format is used.

### **3.4. For my risk management plan to be submitted after 10 January 2013, what format should I use? (New November 2012)**

All new or updated RMPs submitted on or after 10 January 2013, either as a stand-alone update or within a relevant procedure starting thereafter should follow the format and content of the new template, which can be found on the [EMA website](#).

For the centralised procedure, initial marketing authorisation applications or extension of marketing authorisation applications containing a RMP submitted before 10 January 2013 and submitting responses to either the List of Questions (D121) or List of Outstanding Issues (D181) after 10 April 2013 should include an updated RMP within these responses that implements the new template.

All other post-authorisation procedures containing an RMP submitted before the 10 January 2013 do not have to provide an updated RMP implementing the new template within responses to a Request for Supplementary Information or List of Question.

For the mutual recognition and decentralised procedures, any question in relation to the detailed content of an RMP should be clarified and agreed with the RMS.

### **3.5. Will a summary of my RMP be published?**

Marketing authorisation holders (MAHs) are reminded that a summary of the RMP will be published on the European medicines web-portal for the centrally authorised medicinal products and on the national medicines web-portals for the nationally authorised medicinal products. This requirement also applies to existing medicinal products with an RMP. The summary of the RMP will follow the new format and content as set out in the Commission Implementing Regulation and as detailed in the GVP Module V. Guidance for the preparation of the RMP summaries and a detailed plan for publication of RMP summaries will be provided in due course.

### **3.6. Do I need to submit an RMP for my traditional herbal medicinal product?**

The submission of a risk management plan is not required for an application for a traditional-use registration.

For other herbal medicinal products not falling within the scope of the traditional-use registration, an RMP will be required for any initial marketing authorisation applications after 2 / 21 July 2012.

### ***3.7. Do I need to submit an RMP for my homeopathic medicinal product?***

The submission of a risk management plan is not required for homeopathic medicinal products registered via the simplified registration procedure.

For other homeopathic medicinal products not falling within the scope of the simplified registration, an RMP will be required for any initial marketing authorisation applications after 2 / 21 July 2012.

## **4. Non-interventional Post-Authorisation Safety Studies (PASS)**

### ***4.1. Do the new procedures for the PASS protocol, amendments and final study report apply to my non-interventional PASS when submitted after 2 / 21 July 2012?***

The new procedures for submission and assessment of non-interventional PASS protocol, substantial amendments and final study results as provided for in Articles 107n to 107q of Directive 2001/83/EC only apply to PASS studies which have been imposed after 2 / 21 July 2012 as a condition to the marketing authorisation. Such studies shall be identified in the RMP. For the CAPs, they will also be incorporated in the Annex II of the marketing authorisation. For the CAPs it means non-interventional PASS imposed through a Commission decision issued after 2 July 2012 including those with an opinion which may have been adopted in the months just before July 2012. For NAPs, it is anticipated that it will be reflected in the national decision to the marketing authorisation.

### ***4.2. How will MAHs be encouraged to conduct joint studies?***

Where there is a need for a joint PASS to be conducted involving more than one medicinal product, the national competent authority or the EMA will encourage the agreement of the concerned marketing authorisation holders in developing a single protocol for the study and conducting the study jointly. The national competent authority or the EMA may impose as a condition of the MA either a common core protocol or key elements within a protocol which the concerned marketing authorisation holders will have to implement within a timescale laid down by the request.

### ***4.3. In which format should I submit the protocol of my PASS after 2 / 21 July 2012 ? (Update November 2012)***

As set out in the Commission Implementing Regulation, the new format and content for the protocols, abstracts and final study reports for non-interventional PASS imposed as a condition to the marketing authorisation shall apply from 10 January 2013. However, in the absence of pre-existing guidance for the format of PASS protocols, MAHs are strongly encouraged to follow the new format and content as set out in the template ["Guidance for the format and content of non-interventional post-authorisation safety studies"](#) published on the EMA website.

#### **4.4. In which format should I submit the study results of my PASS? Would the Abstract suffice? (New November 2012)**

The Commission Implementing Regulation provides in Annex III a structure which MAHs have to follow when submitting abstract and final study report to competent authorities and the Agency.

#### **4.5. How will individual national requirements for PASS information be communicated to MAHs? (Update July 2012)**

The Member States' requirements for the transmission of information on non-interventional PASS initiated, managed or financed by MAHs voluntarily or pursuant to an obligation can be found as an [annex](#) to the GVP Module VIII.

These requirements do not cover the situation of studies conducted in only one Member State where that Member State requests the study according to Art 22a of Directive 2001/83/EC, in which case the MAH shall submit the draft protocol and the other study information to the national competent authority of the Member State in which the study is conducted.

These tables cover the requirements for transmission of information to national regulatory authorities, but not to ethics committees, national review boards or other bodies in place according to national legislation.

#### **4.6. Will I have to register my PASS? (Update November 2012)**

Article 38 of Commission Implementing Regulation requires that the date of registration of the study in the European register of studies is provided in the final report of results of non-interventional PASS imposed as an obligation. This requirement includes PASS imposed as specific obligation as part of a marketing authorisation under exceptional circumstances and conditional marketing authorisation.

The Agency will have to make public on the European medicines web-portal, protocols and public abstracts of PASS falling within the scope of the new procedures involving the PRAC. In order to achieve this level of transparency, MAHs should have information on the study, including the study protocol, entered prior to the start of data collection into the [electronic register](#) of non-interventional post-authorisation safety studies which is maintained by the Agency (please see question 4.7).

Non-interventional PASS which are initiated, managed or financed voluntarily by a MAH and which are required in the RMP to further investigate safety concerns or to evaluate the effectiveness of risk minimisation activities, or any other PASS should also be entered into the EU PAS Register in order to support the same level of transparency, scientific and quality standards. For these studies, many national competent authorities also accept that registration of the study in the EU PAS Register/[ENCePP E-register](#) may be used as the method to notify the national competent authority of PASS information. For further information on these new requirements please refer to the GVP Module VIII ,and its Annex – [Post-authorisation safety studies Member States' requirements for transmission of information on non-interventional post-authorisation safety studies](#).

This is without prejudice of any national rules on submission/registration.

#### **4.7. Where should I register my PASS? (Update November 2012)**

The EMA will establish and maintain an EU PAS (Post-Authorisation Studies) register allowing to register non-interventional PASS studies, as described in GVP Module VIII. Before the EU PAS register is fully operational, studies should be registered in the [ENCePP E-register](#) of studies. All PASS already



registered in the ENCePP E-register will be included in the EU PAS register. The EMA will send an acknowledgment that a submission has been received, with the date of the registration and the registration number.

#### ***4.8. Is the ENCePP website amenable to receiving an Extensible Markup Language (XML) file that encodes the values for the fields required for registration? (New November 2012)***

The ENCePP E-Register of studies must be populated via the data entry form and it does not accept XML files for upload.

#### ***4.9. Are there requirements for ongoing maintenance of the study record in the ENCePP E-register (e.g. timeframe for updating fields based on amendments to the protocol) ? (New November 2012)***

Data should be kept up to date at all times and changes should be made within 2 weeks following the date of the amended protocol at the latest. These updates may be done via the 'edit' function as described in the document titled '[EU PAS Register Guide](#)' which explains how the ENCePP E-register can be populated to act as the EU PAS Register.

##### Updates to protocols:

The study protocol should be provided before the start of data collection. Where prior publication of the protocol could threaten the validity of the study or the protection of intellectual rights, a study protocol with redactions may be entered into the register prior to the start of data collection. Further information about the requirements for the registration of PASS is available in the GVP Module VIII, Chapter VIII.B.4.

If the full study protocol is uploaded, this can be made publicly available immediately, or at the end of the study only. There is no limit to the number of latest versions of the study protocol that can be uploaded in the system. No changes can be made to the "Initial" document throughout the history of the study record once it has been uploaded and submitted. Within Edit mode (Edit a Study) if a "Latest" version has been uploaded, this can be overwritten as often as necessary with a newer version, but only the very latest version will be visible.

##### Updates to timelines:

A study may have the status "*planned*", "*ongoing*" or "*finalised*"; the database foresees five different study timelines, three of which are mandatory:

**Date when funding contract was signed:** when the planned or the actual date is entered, the status of the study will be "*planned*";

**Start date of data collection:** when the actual date is entered, the status of the study will change from "*planned*" to "*ongoing*";

**Date of final study report:** when the actual date is entered, the status of the study will change from "*ongoing*" to "*finalised*".

Unless the relevant "actual dates" have been entered, automatic reminders are sent 30 days after the planned date for the start of data collection, and 30 days after the planned date of the final study report.

#### **4.10. What is the process for correcting a data entry error in the registration questionnaire? (New November 2012)**

Once the entry has been submitted and accepted, errors may be corrected via the 'edit' function. Prior to submission, errors may be corrected via the function 'Resume draft application'. Both procedures are described in the document titled '[EU PAS Register Guide](#)' which explains how the ENCePP E-register can be populated to act as the EU PAS Register.

#### **4.11. Can a pharmaceutical company register a study in the ENCePP E-registry, which is acting as the EU PAS register, without being a member of ENCePP? (New November 2012)**

The ENCePP E-Register is open to register all PAS regardless of whether there is an application for an ENCePP study seal or whether the research centre participates in the ENCePP network. In order to add a study you simply need to click on the button 'Add a study' on the [ENCePP homepage](#). You will then be guided through the registration process. The process is also described in more detail in the document "[EU PAS Register Guide](#)" which can be downloaded from the ENCePP website.

The E-Register contains information on the study objectives, the main methodological aspects, administrative details (including study timelines and sources of funding), and associated key documents, including study protocols and study results where available. The full questionnaire comprises 19 questions spread over 4 pages, and a [pdf version](#) may be downloaded from the ENCePP website; mandatory information is marked with an asterisk. It is mandatory to enter the name of the lead investigator and full contact details for scientific and public enquiries.

#### **4.12. Could only Principal Investigators register studies on the website? Or can a designated individual from a company register the study? (New November 2012)**

Any designated individual may register the study.

#### **4.13. What should be done in cases where no Primary/Lead Investigator has been delegated by the sponsor/pharmaceutical company? (New November 2012)**

The (primary) lead investigator is the main contact for a registered study. In situations where no (primary) lead investigator has been nominated by the sponsor the contact details of the person in charge of the conduct of the study should be entered in the respective fields. The staff member of a pharmaceutical company or institution who is entering the study details into the E-Register should provide his/her contact details under the contact for scientific or public enquiries.

## **5. Periodic Safety Update Reports (PSUR) and list of European Union Reference Dates (EURD).**

### **5.1. What procedure will be followed for the assessment of my PSUR as of July 2012?**

The single assessment procedure involving only nationally authorised medicinal products will not start in 2012. The EMA will communicate further information in 2013.

The procedure for the different types of products is summarised below:

- For a single centrally authorised medicinal product (i.e. for a substance or combination of active substances contained in only one medicinal product which is centrally authorised), any PSUR submitted as of 2 July 2012 will follow the new procedure involving the PRAC as detailed in the GVP Module VII.
- For several centrally authorised medicinal products containing the same active substance or combination of active substances and where the submission dates are harmonised, the single assessment procedure involving the PRAC will be followed.
- From when the EURD list becomes binding, where centrally and nationally authorised medicinal products contain the same active substance or combination of active substances, the single assessment procedure involving the PRAC will be followed.
- Where nationally authorised medicinal products containing the same active substance or combination of active substances are authorised in more than one Member State and follow already the current worksharing scheme (WS), please refer to [HMA website](#) where arrangements for the assessment of these PSURs is provided until the single assessment procedure involving the PRAC is implemented.
- For nationally authorised medicinal products containing the same active substance or combination of active substances and which are authorised in more than one Member State but which are not covered by the current WS scheme, the assessment of the PSUR remains at an individual national level until the single assessment procedure involving the PRAC is implemented.

Please note that for purely nationally authorised medicinal products identified by the MAH as not authorised in more than one Member State, the assessment of the PSUR will remain at an individual national level as it is outside the scope of the single assessment procedure defined in the legislation.

### ***5.2. In which format should I submit my PSUR after 2 / 21 July 2012? (Update July 2012)***

As set out in the Commission Implementing Regulation, the new format and content of PSUR shall apply from 10 January 2013. The transitional period will apply according to the PSUR submission date and not to the data lock point. PSURs with submission date after the transitional period has elapsed should follow the new format and content established in the Commission Implementing Regulation.

During the transitional period, applicants and marketing authorisation holders can either use the old (Volume 9A) or new (Commission Implementing Regulation) format and content for the PSUR irrespective of the type of procedure followed for the assessment. During the transitional period, summary bridging reports and PSUR addendum reports in accordance with the Volume 9A are also acceptable.

PSURs, summary bridging reports and PSUR addendum reports submitted in accordance with the old format (Volume 9A) during the transitional period, will have to incorporate a critical evaluation of the benefit-risk balance either in the PSUR, summary bridging reports and PSUR addendum reports or in an attachment to the cover letter.

### ***5.3. Do I need to include line listings in my PSUR?***

PSURs prepared under the new format and content will not contain line listings. However the MAH may have to provide them upon request of the EMA or the national competent authorities.

During the transitional period, PSURs submitted with the old format and content, as per Volume 9A should contain line listings.

#### **5.4. What are the timelines for the submission of PSURs during the transitional period? (update November 2012)**

PSURs irrespective of whether it follows the old or the new format should be submitted within 70 or 90 days from the data lock point as established in GVP Module VII which is as follows:

- within 70 calendar days of the data lock point for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point for PSURs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs requested by competent authorities will be normally specified in the request, otherwise the ad hoc PSURs should be submitted within 90 days of the data lock point.

When applying the 60-day rules for PSUR submission with a DLP before 2 / 21 July, if the submission date falls after 2 / 21 July, then the PSUR should be submitted in accordance with the new requirements described above.

#### **5.5. How will regulators assess the EEA and non-EEA non-serious cases?**

The legislation does not require the submission of suspected non-serious ADRs from outside the EEA to EudraVigilance and there is no legal reference in the legislation which requires the EEA non-serious adverse reaction cases to be reported to EMA during the transitional period for ADR reporting until the centralisation of the reporting to EudraVigilance after the EudraVigilance audit.

MAHs have the responsibility to include non-serious cases (worldwide) in the PSUR summary tabulations, to assess these non-serious cases together with the rest of the safety information, communicate the conclusions of that analysis to the regulators, when applicable, under the appropriate procedure and integrate those conclusions in the relevant section(s) of the PSUR.

National Competent authorities in the Member States may receive information for non-serious cases directly from healthcare professionals and patients and may request an analysis of non-serious cases to the MAHs when relevant.

Please refer to question 8.1 for requirements for submission of individual expedited reporting of non-serious cases within the EEA.

#### **5.6. How and to whom should I submit my PSUR? (update November 2012)**

Until the EMA delivers the new PSUR repository, MAHs shall submit the PSUR to all competent authorities of the Member States in which the medicinal product is authorised.

Specifically, the submission should be made in accordance to the document "[Requirements for submission of PSURs for CAPs and NAPs during the transitional period](#)" published on the EMA website.

For CAP, the [eCTD format](#) will continue to apply.

#### **5.7. Until the EURD list is published and becomes binding, for my generic medicinal product, the PSUR cycle is specified as a condition to the**

## ***marketing authorisation, should I continue to submit PSURs? (Update November 2012)***

For generic medicinal products authorised under the legal basis of Article 10(1) of Directive 2001/83/EC, standard statement referring to the PSUR cycle of the reference medicinal product may have previously been included in the MA for clarification purpose. In the context of the new pharmacovigilance legislation, such standard wording on PSUR cycle should no longer be regarded as a condition to the MA, nor an obligation to submit routine PSURs as of 2 / 21 July 2012.

For generic medicinal products for which the PSUR cycle, specified as a condition, deviates from the reference medicinal product, the MAH should continue to submit PSURs accordingly until the EURD list becomes binding (see question 5.11).

In addition, a national competent authority in a Member State or the Commission/EMA may at any time request the submission of a PSUR for a generic medicinal product on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted. In order to ensure a harmonised approach at the level of the European Economic Area (EEA) in terms of PSUR requests and PSUR submissions for products not required to submit routine PSURs, the NCAs in association with the Agency have compiled a "*List of nationally approved substances for which PSURs are required for generic medicinal products during the transitional period*" (i.e. until the EURD reference dates list becomes mandatory in April 2013). The NCAs consider that during the transitional period up to 1<sup>st</sup> April 2013, PSURs for generics will be required for the substances listed on pharmacovigilance concerns. For more details on this transitional list, please refer to the [CMDh website](#).

When the EURD list becomes binding, some generics may require a variation to either remove a previous standard PSUR statement or to align with EURD list, as appropriate (see question 5.15).

### ***5.8. Do I have to submit a PSUR for my medicinal product containing a well established substance?***

For medicinal product containing a well established substance, the requirement to submit a PSUR is only waived for those authorised in accordance with Article 10a of Directive 2001/83/EC. Medicinal products containing a known substance authorised through another legal basis are required to submit PSURs.

### ***5.9. Do I have to submit a PSUR for my herbal or homeopathic medicinal product?***

For herbal and homeopathic medicinal products, the requirement to submit PSUR is only waived for those traditional herbal and homeopathic medicinal products registered through the simplified registration procedure as respectively referred to in Articles 16a and 14 of Directive 2001/83/EC. This derogation to submit PSURs for traditional herbal and homeopathic medicinal products registered through the simplified registration procedure applies unless PSUR submission is requested by a national competent authority in a Member State or the Commission/EMA on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation/registration has been granted, or the substance is included in the EURD list.

### **5.10. When will the EURD list come into force? (Update November 2012)**

The EURD list will come into force 6 months after its publication as final i.e. after adoption by the CHMP and CMDh following consultation of the PRAC. The list was first published on 1<sup>st</sup> October 2012 and will be binding from 1<sup>st</sup> April 2013.

### **5.11. Do I have to continue to submit my PSUR until the EURD list comes into force? (Update November 2012)**

If the medicinal product does not fall within the categories of medicinal products waived by the legislation of the obligation to submit PSUR i.e. generics in accordance to Article 10(1), well-established use in accordance to Article 10a, homeopathics simplified registration in accordance to Article 14 and traditional herbals in accordance Article 16a of Directive 2001/83/EC, marketing authorisation holders should continue to submit PSURs in accordance with the current PSUR cycle of the medicinal product, until otherwise specified in the EURD list which will take effect 6 months after its publication as final.

Until 1<sup>st</sup> April 2013 when the EURD list becomes legally binding, MAHs of generics (authorised under Art 10(1) of Directive 2001/83/EC), well-established use (authorised under Art 10a of the Directive), homeopathic (simplified registration in accordance to Article 14 of the Directive) and traditional herbals (in accordance to Article 16a of the Directive) should not be submitting PSURs if there is no explicit condition in the marketing authorisation or there is no request from a national competent authority/EMA. Please note that on the latter, the NCAs in association with the Agency have compiled a "List of nationally approved substances for which PSURs are required for generic medicinal products during the transitional period" (i.e. until the EURD reference dates list becomes mandatory in April 2013) in order to ensure a harmonised approach at the level of the European Economic Area (EEA) in terms of PSUR requests and PSUR submissions for such products. For more details on this transitional list, please refer to the [CMDh website](#). In addition, in case a PSUR statement is specified in the MA for generic medicinal products (i.e. Annex II for centrally authorised products) if the PSUR cycle differs from the reference medicinal product, the MAH should continue to submit PSURs accordingly until the EURD list becomes binding (see Question 5.7). As of 1<sup>st</sup> April 2013, MAHs for those products should submit PSURs if requested in the EURD list.

The draft EURD list dated 4 April 2012 was published for consultation purposes and is not legally binding. Therefore no reference should be made to this draft list. The [1<sup>st</sup> EURD list](#) adopted by the CHMP/CMDh was published in the EMA website on 1<sup>st</sup> October 2012. Modifications of the list will be published regularly and the modifications will become legally binding 6 months after their publication.

### **5.12. Do I have to submit a PSUR if my medicinal product is not on the EURD list?**

If the active substance contained in the medicinal product is not listed on the EURD list, the MAH should continue to submit PSUR according to the condition in the MA if any, otherwise according to the standard submission cycle (i.e. 6-monthly, yearly and thereafter 3-yearly) unless the medicinal product is a generic, well-established authorised under article 10a of Directive 2001/83/EC, homeopathic simplified registration and traditional-use registration without conditions in the MA. In addition, PSURs shall also be submitted upon request of national competent authorities or the Commission/EMA.



### **5.13. Are the PSUR worksharing and synchronisation lists still applicable?**

Until the single assessment starts for nationally authorised medicinal products, the current PSUR worksharing scheme will continue. (See [HMA website](#) where current arrangements can be found and an update of the process will be published).

Thereafter, the PSUR worksharing and synchronisation will stop with the operation of the single PSUR assessment procedure for NAPs.

### **5.14. If the PSUR cycle of my medicinal product is changed as per the EURD list, can I submit my PSUR according to the new Data Lock Point (DLP) without submitting a variation? (Update November 2012)**

MAHs should follow the new PSUR cycle as defined in the EURD list, independently of a higher or lower frequency than the current one. However, in case the PSUR cycle is stated in the marketing authorisation of a medicinal product, a variation will have to be submitted to align the MA in line with EURD list. For centrally authorised products, please refer to the [Implementation plan for the update to Annex II of the QRD template](#).

### **5.15. Which variation classification should apply to align the PSUR frequency in my marketing authorisation with the EURD list? (Update November 2012)**

As set out in the legislation the MAH will have to vary their marketing authorisation where the PSUR cycle is specified in the MA and will need to be brought in line with the EURD list. Instead of specifying the PSUR frequency, PSUR statements cross-referring to the EURD list will be mentioned (in the Annex II for CAP) in order to avoid the need to submit variation when there will be changes to the EURD list. For centrally authorised products, please refer the [QRD templates](#) updated in November 2012.

In order to facilitate the implementation pending the publication of the final revised variation classification guideline, the CMDh issued in accordance with Article 5 of Regulation (EC) No 1234/2008, a recommendation on classification of an unforeseen variation for change in the PSUR frequency or date of submission, which can be found on the [CMDh website](#). It is classified as a type IA<sub>IN</sub> variation.

For centrally authorised products, an [implementation plan](#) has been published on the EMA website providing further details.

### **5.16. When will the single EU assessment start?**

The procedure involving the PRAC for PSUR assessment for CAPs will start in July 2012. In contrast, the single assessment procedure involving only nationally authorised medicinal products will not start in 2012. The EMA will communicate further information in 2013. Please see question 5.1.

### **5.17. Does every PSUR assessed by PRAC need to go to CHMP or CMDh? (Update July 2012)**

In case of any regulatory action i.e. variation, suspension or revocation of the marketing authorisation, the PRAC recommendation adopted in accordance with the new procedure for a single CAP or the single PSUR assessment procedure will be transmitted to the CHMP if it includes at least one CAP or to the CMDh if it includes only NAPs.

In case the PRAC adopts a recommendation on the maintenance of the marketing authorisation, there is no requirement to transmit such recommendation to the CHMP or CMDh and the procedure ends with the adoption of the PRAC recommendation.

### **5.18. Which PSUR cycle should my medicinal product follow for marketing authorisations granted just after 2 / 21 July 2012? (New July 2012)**

Marketing authorisation holders covered by Article 107b of Directive 2001/83/EC or Article 28(2) of Regulation (EC) 726/2004 have to submit PSURs from the date of authorisation. As set in the new legislation, the frequency with which the PSURs are to be submitted shall be specified in the marketing authorisation.

For medicinal products for which the application was submitted before 2/21 July 2012 but the marketing authorisation was granted in the months following the entry into force of the new legislation, the decision on the granting of the marketing authorisation may not yet specify the PSUR cycle or include a cross-reference to the EURD list.

The legislation provides rules only for those marketing authorisations which were granted before 2/21 July (Article 107c(2) of Directive 2001/83/EC) and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation. By analogy the same rules should apply for the PSUR cycle of marketing authorisation granted after 21 July 2012 but submitted before that date. Consequently, PSURs shall be submitted to the national competent authorities immediately upon request or in accordance with the following frequency:

- Where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;
- Where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

This frequency applies until otherwise specified in the EURD list or in the individual marketing authorisation.

### **5.19. If the data lock point (DLP) of my PSUR is before 2 / 21 July 2012 but the submission date is due after July 2012, am I still required to submit a PSUR for products exempted from the obligation to submit routine PSUR? (New July 2012)**

For medicinal products that have a derogation from routine PSUR provision (i.e. generic, well-established use authorised under article 10a of Directive 2001/83/EC, homeopathic simplified registration and traditional-use registration without conditions in the MA, see question 5.7), the derogation applies as of 2 / 21 July 2012 even where the DLP was prior to 2/21 July but the submission date was due after 2/21 July.

### **5.20. Do I have to submit a PSUR for my hybrid medicinal product? (New July 2012)**

Medicinal products authorised in accordance with Article 10(3) of Directive 2001/83/EC (hybrid application) irrespective of the change applied for (e.g. new strength, new route of administration, etc) are not exempted from the obligation to submit PSUR (see question 5.21 for MRP and DCP products) therefore PSUR submissions are required for hybrid medicinal products.

**5.21. For my product authorised as a generic/hybrid, whom should I contact to establish the corresponding PSUR requirements? (Update November 2012)**

For generic/hybrid medicinal products authorised through the decentralised / mutual recognition procedures, the requirements for a PSUR should be in accordance with those set by the RMS.. In case of doubts, please contact the RMS and for centrally authorised medicinal products, please liaise with the Agency through the PTL of your product to clarify.

**5.22. In the PSUR work sharing scheme, should I still submit a Core Safety Profile (CSP) at the time of the PSUR submission? (New July 2012)**

During the transitional period and up to 10 January 2013 in accordance with Commission Implementing Regulation, a proposal for a CSP should be submitted if the PSUR is submitted in the 'old' format (Volume 9A). For new format PSURs, CSPs are no longer required; please see GVP Module VII.B.4 for the reference documentation to include under the new format.

**5.23. Will existing CSPs be updated? (New July 2012)**

As the new format for PSUR benefit-risk evaluation is introduced, existing CSPs will not be updated.

**5.24. Where will the PSUR worksharing assessment outcome be made available? (Update November 2012)**

The PSUR worksharing assessment is an informal process that predated the new pharmacovigilance legislation. It is distinct from the single assessment procedure conducted by the PRAC.

The outcome of the worksharing assessment will be published on the [HMA webpage](#) dedicated to the PSUR Worksharing Project and on the [CMDh website](#).

MAHs should review the information published and if amendments to the Product Information are needed, an appropriate variation should be submitted.

**5.25. Why are some DLPs included in the EURD list so far in the future? (New November 2012)**

The PSUR frequencies and DLP included in the EURD list have been defined by the NCAs following a risk based approach. These have subsequently been adopted by the CHMP and CMDh following consultation of the PRAC.

It should be noted that DLP put in the long-term future are likely to be amended to take into account any need to re-evaluate the risk-benefit profile of a substance/product earlier or, in particular, in case of emergence of any pharmacovigilance concerns.

**5.26. Do I have to submit a PSUR if my combination product is not on the EURD list but one or more standalone components are listed? (New November 2012)**

If the specific fixed combination medicinal product is not listed on the EURD list and if the medicinal product does not fall within the categories of medicinal products exempted by the legislation of the obligation to submit PSUR, the MAH should continue to submit PSURs according to the condition in the MA if any, otherwise according to the standard submission cycle (i.e. 6-monthly, yearly and thereafter

3-yearly). Stakeholders can request the inclusion of the fixed combination in the EURD list for reasons related to public health, in order to avoid duplication of assessment or in order to achieve international harmonisation. Instructions on how to submit comments and requests to amend the EURD list can be found on the [EURD list webpage](#).

**5.27. As a MAH of products referred to in Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC, how should I communicate any safety information to National Competent Authorities and the Agency? (New November 2012)**

Products referred to in Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC are exempted from routine submission of PSURs. Therefore, alternative mechanisms such as signal management and emerging safety issues channels should be used to communicate relevant new safety information to regulatory authorities (see GVP Module VI and Module IX). Additionally, product information should be kept up-to-date in line with Article 16(3) of Regulation (EC) No 726/2004 / Article 23(3) of Directive 2001/83/EC by submitting the appropriate variations taking account of the current scientific knowledge, which includes the conclusions of the assessment and recommendations made public by means of the EMA and National Competent Authority websites and, when available, the European medicines web-portal.

**5.28. Do I have to submit a PSUR for my medicinal product authorised under the older Directive? (New November 2012)**

Medicinal products which have been authorised through the equivalent legal basis as the current Articles 10(1) and 10a legal basis before the re-codification of the Directive 2001/83/EC i.e. respectively Article 4.8 a(iii), first paragraph (essential similarity) of Directive 65/65/EEC / 10 a(iii), first paragraph of Directive 2001/83/EC and Art 4.8 a(ii) (well established use) of Directive 65/65/EEC / 10.1 a(ii) of Directive 2001/83/EC are, by analogy, not required to submit PSUR unless there is a specific condition in the authorisation or there is an indication in the EURD list that PSUR submission is required, or in response to a specific request.

## **6. Literature monitoring**

### **6.1. When will the EMA start to monitor selected medical literature?**

As per the plan for implementation of the pharmacovigilance legislation by the EMA published on the EMA website, the monitoring of selected medical literature for certain active substances will not start in 2012. Further information on the start of this activity will be communicated in 2013.

The stakeholders will be consulted in due time on guidance for the conduct of the literature monitoring activities.

## 7. Product Information and the black symbol

### **7.1. When will I have to implement in the product information of my medicinal product the new text to encourage the reporting of suspected adverse reactions and, as applicable, the black symbol with the specific statements? (Update November 2012)**

The intention is to update the QRD templates for CAPs and NAPs that will include all the new requirements in the summary of product characteristics (SmPC) and package leaflet (PL) including:

- The black symbol and standard statements for products subject to additional monitoring.
- The statement to encourage the reporting of suspected adverse reactions for patients and healthcare professional applicable to all medicinal products.

A public consultation exercise was performed on these templates.

Considering that the black symbol has to be selected by the European Commission after recommendation from the PRAC, the updated QRD templates will be published only after the selection of the symbol.

The selected symbol and standard statements will have to be included in the SmPC and PL of the medicinal products subject to additional monitoring. It is expected that the introduction of the black symbol will require the submission of a variation.

Further guidance and timelines to implement the new QRD templates including the black symbol and standard statements on the additional monitoring and on the reporting of suspected adverse reactions will be given at the time of publication of the revised QRD templates planned for Q2 2013.

The update to the QRD templates in November 2012 only affects Annex II to take into account the new requirements for the PSUR and the granularity of the conditions set out in the pharmacovigilance legislation. For more information regarding this update, please see [QRD template and implementation plan](#).

### **7.2. Which version of the QRD templates should I use as of July 2012? (Update November 2012)**

The applicants should follow the most up-to-date version available of the QRD templates for the submission of their initial marketing authorisation application and post-authorisation applications affecting the product information.

## 8. Adverse Drug Reaction (ADR) reporting and signal management

### **8.1. Are there any Member State requirement for reporting of non-EEA serious and EEA non-serious ICSRs?**

Please refer to [the table](#) that compiles the Member State and EMA requirements for any submission of individual expedited reporting of serious cases from outside the EEA and non-serious cases within the EEA during the transition period from July 2012 to the switch to the centralised reporting to EudraVigilance.

Please refer to question 5.5 for how will regulators assess the non-EEA non-serious cases.

**8.2. Is it a requirement to record in the global safety database abuse, misuse, use outside the terms of MA, which does not lead to an adverse reaction? (Update November 2012)**

There is no requirement to submit individual case safety reports of overdose, drug interactions, abuse, misuse, off label use, pregnancy and lactation exposure if not linked to a suspected ADR i.e. a response to a medicinal product which is noxious and unintended.

However to be able to conduct signal detection, to continuously monitor the benefit-risk balance, to produce PSURs and to inform regulators of any changes to the benefit-risk balance, the MAH will have to have procedures in place to collect and record relevant information.

**8.3. Is it planned to set up specific tools to allow reporting to EudraVigilance, particularly for SME?**

There is already a specific tool available through the [EVWEB](#).

**8.4. Access to MedDRA-terms: How can a SME apply for access and is it free of charge?**

MedDRA is free within EVWEB for Small & Micro-sized enterprises, but not for medium-sized enterprises. Information on the MedDRA licensing policy and EudraVigilance is available from the [EV website](#).

**8.5. Should the protocol of any post-authorisation study, even if not aimed at assessing safety, require the investigators to collect all adverse events and report them to the MAH? (New July 2012)**

GVP Module VI, Chapter VI.C.1.2. - Interface with post-authorisation studies - states "...marketing authorisation holders should have in place a system to collect full and comprehensive case information and to evaluate that information in order to determine whether the collected adverse events are possibly related to the studied (or supplied) medicinal product and should be classified and processed as ICSRs of suspected adverse reactions."

Therefore, all adverse events should be collected by the MAH and assessed as to whether or not they are suspected adverse reactions.

**8.6. In case of adverse events actively sought from patients, should the MAH systematically ask the patient about his/her opinion on causality? (New July 2012)**

GVP Module VI, Chapter VI.C.2.2.11. - Reports from patient support programmes and market research programmes - states "Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (See VI.C.2.2.2) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product."

GVP Module VI, Chapter VI.C.2.2.2. - Solicited reports - states "Marketing authorisation holders should therefore exercise due diligence in establishing such system, in following-up those reports (See VI.B.3) and in seeking the view of the primary source as regard the causal role of the studied (or supplied)



medicinal product on the notified adverse event." Therefore, the MAH should exercise due diligence in asking the primary source for their opinion on causality.

**8.7. If no causality assessment is provided by the patient, should the report be considered as a suspected reaction by default (since the primary-source causality is missing) or is the MAH's causality assessment sufficient to decide whether the report is a suspected adverse reaction or a non-reportable adverse event? (Update November 2012)**

GVP Module VI, Chapter VI.A.2.1.1.(spontaneous reporting) - For regulatory reporting purposes, as detailed in the ICH-E2D guideline, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all spontaneous reports notified by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

GVP Module VI, Chapter VI.C.2.2.11. - Reports from patient support programmes and market research programmes - states "Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (See VI.C.2.2.2) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product".

GVP Module VI, Chapter VI.C.2.2.2. - Solicited reports - states "Marketing authorisation holders should therefore exercise due diligence in establishing such system, in following-up those reports (See VI.B.3) and in seeking the view of the primary source as regard the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the marketing authorisation holder should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR, which should be reported to the competent authorities."

**8.8. Does EudraLex – Volume 9A – Questions and answers on implementation of exchange of Individual Case Safety Reports (ICSRs) electronically, version 5.4 (EMA/46003/2011) remain applicable after publication of GVP VI? (New November 2012)**

The Good Vigilance Practice (GVP) modules published in June 2012 have integrated, where applicable, the topics addressed in this Questions and Answers (Q&As) document. Stakeholders should adhere to the recommendations provided in the relevant GVP modules which supersede this Q&A version 5.4.

## **9. Renewals**

**9.1. When will the new requirements as set out in the updated guideline apply?**

As set out in the Commission transitional arrangements, the obligation to submit the renewal application 9 months before the expiry of the marketing authorisation applies to medicinal products for which the marketing authorisation expires after 2 / 21 April 2013.

The new requirements on the content and procedure for a renewal which are set out in the updated guidelines will apply as of 2 / 21 July 2012 and can be found on the [EMA website](#) for the centralised authorised products and on the [CMDh website](#) for the products authorised through the Mutual Recognition and Decentralised procedures. Therefore any renewal applications submitted after 2 / 21

July 2012 will have to comply with the new requirements and will follow the new procedure. PSUR, PSUR addendum, Summary Bridging Report and line listing should no longer be submitted as part of the renewal application. Therefore, in the first months of implementation it is particularly critical that the clinical overview should include relevant information to support the benefit-risk re-evaluation of the medicinal product.

## **9.2. Can I introduce the summary of the pharmacovigilance system within the annual renewal application of my conditional marketing authorisation?**

Please refer to question 2.8.

### **Reference documents:**

- [Regulation \(EC\) No 726/2004](#)
- [Directive 2001/83/EC](#)
- [Commission Implementing Regulation \(EU\) No 520/2012](#)
- Commission [Question on Answers](#) on transitional arrangements concerning the entering into force of the new pharmacovigilance rules
- [Good Pharmacovigilance Practices](#)
- [Plan for implementation of the pharmacovigilance legislation by the EMA](#)

### **Abbreviations**

- ADR – Adverse Drug Reaction
- CAP – Centrally Authorised Product
- CHMP - Committee for Medicinal Products for Human Use
- CMDh – Coordination Group for Mutual Recognition & Decentralised Procedure – human
- CSP – Core Safety Profile
- DCP – Decentralised Procedure
- DDPS – Detailed Description of the Pharmacovigilance System
- DLP – Data Lock Point
- EC – European Commission
- eCTD – electronic Common Technical Document
- EEA – European Economic Area
- EMA – European Medicines Agency
- ENCePP – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

- EU – European Union
- EU PAS Register – EU electronic register of post-authorisation studies
- EURD list – List of European Union Reference Dates and frequency of submission of Periodic Safety Update Reports
- GVP – Good Pharmacovigilance Practices
- HMA – Heads of Medicines Agencies
- ICSR - Individual Case Safety Reports
- MA – Marketing Authorisation
- MAH – Marketing Authorisation Holder
- MEDDRA – Medical Dictionary for Regulatory Activities
- MRP – Mutual Recognition Procedure
- MS – Member State
- NAP – Nationally Authorised Product
- PAS – Post-authorisation Studies
- PASS – Post-authorisation Safety Studies
- PL – Package Leaflet
- PRAC – Pharmacovigilance and Risk Assessment Committee
- PSMF – Pharmacovigilance System Master File
- PSUR – Periodic Safety Update Report
- Q&A – Question and Answer
- QPPV – Qualified Person responsible for Pharmacovigilance
- QRD – Quality Review of Documents
- RMP – Risk Management Plan
- RMS – Reference Member State
- SME – Small & Medium Sized Enterprise
- SmPC – Summary of Product Characteristics
- WS – worksharing
- XEVMPD – eXtended EudraVigilance Medicinal Product Dictionary
- XEVPRM – eXtended EudraVigilance Medicinal Product Report Message