DRUGS COUNCIL
PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH
CYPRUS

Guidance to Marketing Authorisation Holders (MAH) on the new Pharmacovigilance (PV) Legislation

Contents

Guidance to Marketing Authorisation Holders (MAH) on the new Pharmacovigilance (PV) Legislation

Section I. Purpose of this document

The purpose of this guidance document is to offer practical guidance and references for further information, to all applicants applying for a Marketing Authorisation (MA), or to the MAHs for products already authorized in Cyprus. This document is not meant to substitute guidance available by the Commission or the European Medicines Agency (EMA), but rather to make reference to those and collate information into practical steps that MAHs can follow in order to fulfill their new PV obligations. These obligations are stipulated by the new PV Legislation that was transposed into National Legislation in Cyprus and in the decisions taken by the Cyprus Drugs Council.

In cases of conflicting information, provisions of the Directives and Regulations, prevail to guidance and to National Legislation. **Acronyms** are widely used in this document. At the end of the document you may find a complete list of the acronyms used.

Section II. Legislation for Pharmacovigilance (PV)

Table 1 indicates the PV relative legislation

Legislation/Directive/National Law	Brief Description	Link
Directive 2010/84/EC as regards Pharmacovigilance	The Directive amends Directive 2001/83/EC and introduces extensive provisions as to enhance Pharmacovigilance activities for medicinal products for human use. Directive came into force on **21/7/2012** but some provisions are not implemented yet (transitional provisions) or further guidance or development of infrastructure is awaited.	http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm
Directive 2012/26/EU as regards Pharmacovigilance	The Directive amends Directive 2001/83/EC and introduces an automatic procedure at Union level in cases of specific safety issues to ensure that a matter is assessed and addressed in all Member States where the medicinal product is authorised. The Directive also introduces obligations to wholesalers who are importing or exporting to 3rd countries.	http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm
Regulation 1235/2010 as regards Pharmacovigilance	The Regulation amends Regulation 726/2004 and, among others, establishes the PRAC, enhances the Eudravigilance database, etc.	http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm
Corrigendum to Regulation (EU) No **1235/2010**	Corrections to article 16(3)(4) of the Regulation 1235/2010	http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm
Regulation 1027/2012 as regards Pharmacovigilance	The Regulation amends Regulation 726/2004 and provides for the list of medicinal products subject to additional monitoring.	http://ec.europa.eu/health/documents/eudralex/vol

Commission **Implementing Regulation (EU) No 520/2012** on the performance of Pharmacovigilance activities	The Implementing Regulation (IR), as provided by article 108 of the Dir 2010/84/EC, adopts measures for: • PV System Master File • PV Quality Systems • PV Terminology, formats and standards • Eudravigilance database requirements • Electronic submission of ADRs • PSUR and RMP format and contents • PASS format of protocols, etc.	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
Commission **Implementing Regulation (EU) No 198/2013**	Describing the symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring (inverted black triangle) (▼)	http://ec.europa.eu/health/files/eudralex/vol-1/reg_2013_198/reg_2013_198_en.pdf
Cyprus Law amending the basic legislation as regards Pharmacovigilance	Law 63(I) of 2012 amending the basic Law No. 70(I) of 2001 • Adopting Directive 2010/84/EC	http://www.moh.gov.cy/MOH/phs/phs.nsf/All/62625121DD195500C2257A1A003467FE/$file/Νόμος%20που%20τροποποιεί%20τους%20Περί%20Φαρμάκων%20Ανθρώπινης%20Χρήσης-%20Τροποποίηση%20που%20αφορά%20στη%20Φαρμακοεπαγρύπνηση.pdf?OpenElement

Section III. Guidance (main) available to MAHs

Table 2 indicates main guidance available to the MAHs

Guidance	**Brief Description**	**Link**
EMA Website	The website provides a lot of information on the New Pharmacovigilance legislation and includes references to legislation and guidance documents	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad
European Commission (DG Health and Consumers) Website	The website provides a lot of information on the New Pharmacovigilance legislation and includes references to legislation and guidance documents	http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm
Heads of Medicines Agencies (HMA) Website	The website provides a lot of information on the New Pharmacovigilance legislation and guidance offered by the CMDh	http://www.hma.eu/310.html
MHRA Website	The website provides information on the New Pharmacovigilance legislation, as well as a Q&A section and indicates implications to the MAHs.	http://www.mhra.gov.uk/Howweregulate/Medicines/Pharmacovigilancelegislation/index.htm
Eur. Commission: Q&A on transitional arrangements	The document provides guidance on issues, such as: • Renewal Applications • Pending MA at the time of introduction of the directive • PSMF • RMP • PRAC Involvement • PASS	http://ec.europa.eu/health/files/pharmacovigilance/2012_02_qa_phv.pdf
EMA: Q&A to support the implementation of the Pharmacovigilance legislation Nov 2012	The document provides guidance on issues, such as: • Good Pharmacovigilance Practices (GVP) guidelines • Pharmacovigilance system master file (PSMF) and summary of the pharmacovig. system • Risk Management Plan (RMP)	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127658.pdf

	• Non-interventional Post-authorisation safety studies (PASS) • PSUR and EURD list • Literature monitoring • Product information and black symbol • Adverse Drug Reaction (ADR) reporting and signal management • Renewals	
Good Pharmacovigilance Practices (GVP)	Good Pharmacovigilance Practices (GVP)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c
GVP Introductory cover note	Introductory cover note, last updated with finalisation of module XV	See previous column
GVP Module I	Pharmacovigilance systems and their quality systems	See previous column
GVP Module II	Pharmacovigilance system master file	See previous column
GVP Module III	Pharmacovigilance inspections	See previous column
GVP Module IV	Pharmacovigilance audits	See previous column
GVP Module V	Risk management systems	See previous column
GVP Module VI	Management and reporting of adverse reactions to medicinal products	See previous column
GVP Module VII	Periodic safety update report	See previous column
GVP Module VIII	Post-authorisation safety studies	See previous column
	Annex to good pharmacovigilance practices module VIII – Post-authorisation safety studies: Member States' requirements for transmission of information on non-interventional PASS	See previous column
GVP Module IX	Signal management	See previous column
GVP Module XV	Safety communication	See previous column
GVP Annexes	Annex I - Definitions	See previous column
GVP Annexes	Annex II - Templates: Direct healthcare-professional communication	See previous column
EMA Guidance to MAH	- Guidance on RMP - European Union reference dates and frequency of submission of periodic safety update reports (PSUR) - Product-type- and population-specific guidance - Pharmacovigilance practices	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3%23section1
Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to MAH during the interim period	The document presents Member States reporting requirements during the interim period for serious non-EU ICSRs and for non-serious EU ICSRs	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127657.pdf
ICH guideline E2C (R2) Periodic benefit-risk evaluation report (PBRER)	The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved medicinal products that are under further study) among the ICH regions.	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125440.pdf

Section IV. Changes in Applications for the Issue, Renewal or Variation of a Marketing Authorisation (MA)

A. Application for the issue of a NEW marketing authorisation (MA)

Legal basis: Article 8(3), as amended, provides for 2 new requirements for new applications:

1. *Summary of the Pharmacovigilance System (PSMF PhVig System Master File)*
2. *Risk Management Plan (RMP) with a Summary*

1. Summary of the Pharmacovigilance System (PSMF PhVig System Master File)

What information should be included

New applications received from now on, must contain a *Summary of the Pharmacovigilance System* (and **not** a DDPS) in section 1.8.1, which must include:

- Qualified Person for PV (QPPV), i.e. name and contact details [address, telephone number, fax number, email, country (**EEA**)]
- QPPV address where he/she resides (may be a different country than above, but still in EEA)
- QPPV CV (curriculum vitae)
- Location of the Pharmacovigilance System Master File (PSMF) (complete address in EEA)
- A signed statement that the Applicant/Marketing Authorisation Holder (MAH) has the necessary means to fulfill the tasks and responsibilities listed in *Title IX of the Directive 2001/83/EC*

Where should the new data be included?

In section 1.8.1 of the dossier. No specific template is foreseen.

For what type of products

For all legal types of applications, including generic products, a Summary of the PV System as above must be provided. Homeopathic Products registered via the simplified registration procedure and Traditional Herbal Medicinal Products with a traditional use registration are exempted from this requirement *(BUT Note that the requirement to operate a PV system and to maintain and make available on request a PSMF also applies to traditional herbal medicinal products).*

Transitional measures and other information

New applications should be prepared as above and should **not** contain a DDPS. *DDPS variations for existing applications are still required until a Pharmacovigilance System Summary has been introduced, and therefore will continue to be required for some MAs* ***until July 2015.***

Application Form: a new application form will be introduced by NtA WG. For the time being, the existing one must be used.

2. Risk Management Plan (RMP) and RMP Summary

What information should be included

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. *GVP module V* offers further guidance on the required content and format of RMPs.

What is the format of RMP to be included in an application

Guidance on format of the risk management plan (RMP) in the European Union may be found in the relative EMA guidance

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134743.doc

For what type of products

For all legal types of applications, including generic products, a RMP as above should be provided. Homeopathic Products registered via the simplified registration procedure and Traditional Herbal Medicinal Products with a traditional use registration are exempted from this requirement.

Transitional measures and other information

For initial MA applications under evaluation which were submitted before **21 July 2012** and do not contain an RMP, there is no obligation to submit an RMP during the course of the evaluation procedure.

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

For those MAs granted before **21 July 2012** without an existing RMP, there is no obligation to submit a RMP unless requested by the Drugs Council.

When the submission of updated RMP will be enforceable by the Drugs Council

Until the **end of April 2013** new applications without prior update of the RMP will be accepted. The MAHs should commit to submit the appropriate variations within an agreed period.

B. Application for the RENEWAL of a Marketing Authorisation (MA)

What information should be included?

Renewal applications received from now on, must contain:

- **A Pharmacovigilance System Summary** in section 1.8.1 (see Section A above)
- **A benefit-risk evaluation**: Addendum to the Clinical Overview has been expanded and should include a benefit/risk evaluation. *PSURs are no longer required.*
- **An updated Risk Management Plan (RMP)**. Where there are no new data justifying changes to the latest approved RMP, the MAH should provide a *declaration* and confirm that the current approved RMP remains unchanged and applicable.
- **A history of PV Inspections** and a summary of the findings as part of Module 1.2.

Other changes to the Renewal application

- Renewal applications should be submitted **nine (9) months** before the expiry of the MA.
- Submission of PSUR is **no** longer required.

Renewal Application Form

A new Application Form for Renewal is available on our website and HMA Website.

C. Application for VARIATION of a Marketing Authorisation (MA)

PSMF Summary

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. Only below indicated changes (referred in PSMF Summary) will be subject to a Variation Application

a. Introduction or Change of the PV System Summary
b. Changes in the QPPV, including contact details, and/or the location of the PSMF as part of the summary of the PV System

Above new Variations are Type IAIN and both will be submitted under C.I.Z. An updated *variations classifications guideline* will be issued in due course (for more information refer to *CMDh Recommendations* -HMA website).

Risk Management Plan (RMP)

A completely new RMP should be submitted as a type II variation under classification category C.I.z. An update of an already approved RMP should be submitted as a type IB variation under classification category C.I.z. In case the new or updated RMP is a consequence of other variations, e.g. extension of the indication, the RMP may be submitted as part of this variation application without the necessity of a separate variation category. The same

rules apply for the submission of new or updated core RMPs until further guidance will be published (for more information refer to *CMDh Recommendations* -HMA website).

Section V. Pharmacovigilance System Master File

Some key information is given in this Section for PSMF. For complete reference and information, refer to: GVP Module II: PSMF (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123206.pdf) and to the Section I. Table 1 (Legislation) and Section II. Table 2 (Guidance) above.

What is PSMF

The pharmacovigilance system master file (PSMF) definition is provided in *Article 1(28e) of Directive 2001/83/EC* [*A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products*] and the minimum requirements for its content and maintenance are set out in the Commission Implementing Regulation (EU) No 520/2012.

The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in *GVP Module II of the Good Vigilance Practice(s).* The PSMF is modular, with descriptions and lists being organised to show change via a logbook or via change control of lists (annexes). The main contents are described in *GVP Module II.*

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*. It is possible for a MAH to have more than one system (and PSMF) (for an MA or a portfolio of MAs). The pharmacovigilance system master file shall include documents to describe the pharmacovigilance system. The content of the pharmacovigilance system master file should reflect the global availability of safety information for medicinal products authorised in the EU. The content shall be indexed to allow for efficient navigation around the document and follow the modular system described in the *GVP Module II, Chapter II.B.4.* The main principle for the structure of the content of the pharmacovigilance system master file is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes.

Location of PSMF

The pharmacovigilance system master file shall be located (physically) either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates *[IM Art 7(1)].*

Summary of the PSMF

It is a requirement of the marketing authorisation application that summary information about the pharmacovigilance system is submitted to the competent authorities *(refer to Section IV.A.1 above)*

Changes to PSMF and Variations Applications

There is no requirement for variations for changes in the content of the pharmacovigilance system master file. PSMF will be kept up to date by the MAH, without the need of submitting variation applications*. Only for changes to the 'PSMF Summary', Variation Applications should be submitted *(refer to Section IV.C above).*

[In contrast, prior to the introduction of PSMF, updates to DDPS required the submission of variation application, e.g. QPPV change, QPPV contact details change, back up of QPPV, change in the safety database, change in contractual arrangements, topics covered by written procedures, PV sites, (other) (CI.9 of variations classification guideline)].*

What are the contents of GVP Module I PSMF

The above Module provides detailed guidance regarding the requirements for the PSMF, including its maintenance, content and associated submissions to competent authorities, applicable from **July 2012**, during the transition period (as described in *Article 2 of Directive 2010/84/EU and Article 3 of Regulation (EU) No 1235/2010),* and **after 2015.**

When should MAHs introduce 'PSMF Summary' in their MAs

1. For initial MA Applications: At the time of submission *(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 MA and placing of the product on the market)*.
2. For existing marketing authorisations (MAs), in the following cases whichever is the **earlier**
   - At the time of submission of the renewal application *(refer to Section IV.B above) ,*
   - By **21 July 2015.**
   - MAHs may, voluntarily, introduce PSMF Summary by submitting a Variation Application *(refer to Section IV.C above).*

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

Section VI. Risk Management Plan (RMP)

Some key information is given in this Section for RMP. For complete reference and information, refer to:
Module V – Risk management systems
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123208.pdf
and to the Section I, Table 1 (Legislation) and Section II, Table 2 (Guidance) above.

What is a Risk Management System (RMS)
It is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions *[DIR Art 1(28b)].*

What is a Risk Management Plan (RMP)?
A detailed description of the risk management system *[DIR Art 1(28c)].*

What are the obligations of MAHs for minimizing risk of medicines?

- Ensuring that they constantly monitor the risks of their medicines in compliance with relevant legislation and report the results of this, as required, to appropriate Competent Authorities
- Taking all appropriate actions to minimise the risks of their medicines and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicines, and actively updating and communicating it when new information becomes available.

Overview of the parts and modules of the RMP
The RMP is divided into several parts, with the safety specifications of the RMP organised into modules to increase flexibility. In some circumstances some modules may be omitted from the RMP unless requested by the Drugs Council. *(refer to GVP Mod V)*

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

Part VI Summary of the RMP
Part VII Annexes

What is the format of RMP
Guidance on format of the risk management plan (RMP) in the European Union, is given in the relative EMA guidance document:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134743.doc

When a RMP is submitted
***New MAs*:** An RMP is submitted with every new application for a MA, irrespective of the legal basis (i.e. includes generic products), except Homeopathic Products registered via the simplified registration procedure and Traditional Herbal Medicinal Products with a traditional use registration.
***Old MAs with RMP*:** For MAs granted before **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*. An update of an already approved RMP should be submitted as a type IB variation under *classification category C.I.z.*
***Old MAs without RMP*:** For those MAs granted **before 21 July 2012** without an existing RMP, there is no obligation to submit a RMP unless there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product (in which case, the Drugs Council will request the submission of a RMP). A completely new RMP should be submitted as a type II variation under *classification category C.I.z.*

Who evaluates RMPs
The new PRAC will have regulatory oversight of RMPs for products authorised centrally or in more than one Member State and the Drugs Council for nationally authorised products. PRAC will appoint a rapporteur for an individual RMP, who will work with the (co-)rapporteur appointed by the Committee on Medicinal Products for Human Use (CHMP) or with the Reference Member State. Summaries of RMPs shall be made publicly available via web portals.

Updates and Timelines to the risk management plan *(refer to GVP Mod V)*

- If an RMP has been previously submitted by the applicant/MAH for the active substance, any following submissions shall be in the form of an update, unless requested otherwise. Each submission of the RMP will have a distinct version number and date.
- The time schedule for providing "routine" updates to the RMP will normally be included as a condition of the marketing authorisation, or otherwise notified to the MAH by the competent authority.
- If the requirement for providing routine updates to the RMP is not specified as part of the marketing authorisation, routine updates should be provided (unless requested otherwise by the competent authority):
    - annually until the first renewal of the marketing authorisation
    - every three years thereafter.
- It is anticipated that, where a PSUR is also required, the timing for submission of the RMP would be aligned with that of PSUR updates. Unless specified otherwise, when both PSURs and RMPs are required for a product, routine updates to the RMP should be submitted at the same time as the PSUR.
- For medicinal products which have an existing RMP in a format different to that introduced in this guidance, the EMA will publish on its website a timescale by when updates to the RMP should be in the new format.

Section VII. PSUR (Periodic Safety Update Report) and EURD List (EU Reference Dates List)

Details and guidance for the submission of PSURs in the EU, including the list of Union references dates and frequency of submission are provided in ***GVP Module VII***

What are the key changes?
PSUR should fulfill the objective of benefit-risk evaluation reporting in a cumulative manner. There are new evaluation sections to support this approach to integrated analysis, including a section to give an overview on signals (tabulated as new, ongoing or closed). The PSUR should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation. There will be no routine requirement for line listings *[IR Art*

34(4)], however, these may be requested during an assessment. PSUR reporting should be linked to the risk management plans (RMPs) of a medicinal product. The "modular approach" of the PSUR described in GVP Module VII aims to minimise duplication and improve efficiency during the preparation and review of PSURs along with other regulatory documents such as the development safety update report (DSUR) or the safety specification in the RMP, by enabling the common content of particular sections, where appropriate, to be utilised interchangeably across different PSURs, DSURs and RMPs.

Format and Content of PSUR

The format of PSURs shall follow the structure described in the *Implementing Regulation, Article 35*. The new format is given in *GVP Module VII*. *GVP Module VII* provides guidance on the preparation, submission and assessment of PSURs. The required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the *ICH-E2C(R2) guideline* (see reference above in *Section III, Table 2)*.

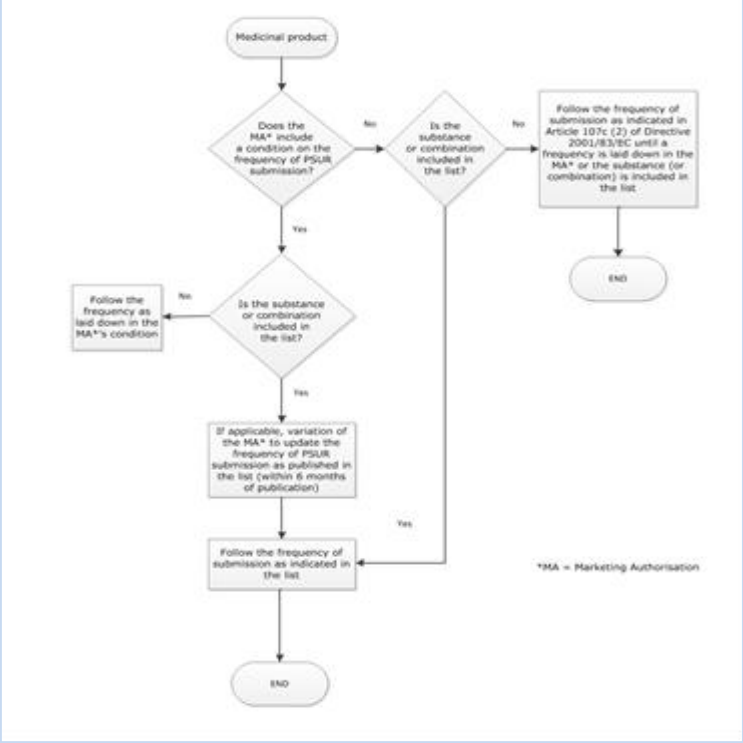
Timelines and submission of PSUR

The submission frequency will be variable and risk based. Marketing authorisation holders for products authorised before **02 July 2012** (centrally authorised products) and **21 July 2012** (nationally authorised products) and for which the frequency and dates of submission of PSURs are (a) not laid down as a condition to the marketing authorisation or (b) determined otherwise in the list of Union reference dates (EURD List, see below) shall submit PSURs according to the following submission schedule *[REG 28(2), DIR Art 107c(2)]:*

- at 6 months intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years,
- then once a year for the following 2 years
- and thereafter at 3-yearly intervals.

Multiple six-monthly reports, summary bridging reports, or addendum reports will not be accepted. The time interval between the data-lock point and submission has also been expanded.

The diagram below (GVP VII Figure VII.2) presents the various scenarios for the submission of PSURs



Submission waiver for Generics and other products

The legislation introduces derogation for routine PSUR reporting for certain products. Unless there is a specific condition in the MA, or it is indicated otherwise in the EURD for the substance concerned, routine PSUR reporting will not be required for medicinal products authorised under the following articles of *Directive 2001/83/EC*:

- Article 10.1 generic
- Article 10.a well-established use
- Article 14 homeopathic medicine
- Article 16a traditional herbal medicine

PSUR Assessment and Transitional period

The new legislation introduces the principle of EU single assessment of periodic safety update reports (PSURs) where a substance is authorised in more than one Member State and establishes the list of European Union Reference Dates (EURD). The single assessment procedure is being implemented in a phased approach.

Until the single assessment procedure is introduced for non-centralised products, the assessment of PSURs for these products will follow procedures currently in place (i.e. EU PSUR worksharing, Mutual Recognition procedures and purely National Procedures).

When infrastructure is made available, the EMA will make the PSURs available to the competent authorities in Member States, members of the Pharmacovigilance Risk Assessment Committee (PRAC), of the Committee for Medicinal Products for Human use (CHMP) and of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and the European Commission **by means of a PSUR repository** *[DIR Art 107b(2)].*

List of European Union reference dates (EURD – DLP Data Lock Points)

For complete information refer to GVP Module VII and to EMA website
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/09/news_detail_001616.jsp&mid=WC0b01ac058004d5c1)

The list of Union reference dates
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/09/news_detail_001616.jsp&mid=WC0b01ac058004d5c1#] and frequency of submission of periodic safety update reports (referred to as the "EU reference dates list" in the GVP Module VII) consists of a comprehensive list of active substances and combinations of active substances sorted in alphabetical order, for which Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the EU reference dates and frequencies determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance and Risk Assessment Committee (PRAC) *[DIR Art. 107c(4)1].* The EU reference dates list has been compiled in order to facilitate the harmonisation of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances subject to different marketing authorisations, authorised in more than one Member State. This will, where appropriate, allow the single assessment of the related PSURs as set out in the new EU pharmacovigilance legislation *[DIR Art. 107e].* The list is a living document, i.e. that it can be amended whenever considered necessary by the PRAC, CHMP or CMDh in response to the emergence of relevant new safety information, newly authorised substances and requests received from the marketing authorisation holders as defined in *[DIR Art 107c(6)]*

The PSUR frequency as published on the EU reference dates list for a given active substance or combination of active substances overrules the submission schedule described in *[DIR Art 107c (2)]* and any conditions related to the frequency of submission of PSURs included in the Marketing Authorisation. This approach is without prejudice to the right of the Cyprus Drugs Council to request the submission of PSURs at any time.

As a result of the publication of the EU reference dates list, any changes to the PSUR submission frequency and DLP will trigger the obligation of the marketing authorisation holders (MAHs) to submit, where applicable, a variation for the products where contradictory requirements are specified in the Marketing Authorisation *[DIR 107c(4) and (6)].*

Aligning products with the PSUR data lock points and frequencies listed in the EURD list

For nationally authorised products and MRP/DCP products authorised before 21 July 2012, for which there was no legal obligation for PSUR frequency of submission, the EURD will become mandatory six months after publication and a variation will not be required to align with the EURD (refer also to the Figure VII.2 above).

Section VIII: PRAC and Products under additional monitoring

(GVP Module X)

Pharmacovigilance Risk Assessment Committee (PRAC)

The newly established Pharmacovigilance Risk Assessment Committee (PRAC), will be meeting monthly and will advise the Committee on Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on safety issues in relation to medicines in the EU. PRAC replaces the Pharmacovigilance Working Party in the current EU regulatory network. The PRAC members will include patient organisations and healthcare professionals, as well as experts from the EU Member states appointed on the basis of their relevant expertise in pharmacovigilance and risk assessment.

Additional monitoring list - inverted black triangle symbol (▼)

One of the requirements of the new pharmacovigilance legislation is the introduction of a European 'additional monitoring' scheme. Medicines included on the additional monitoring list will be subject to more intense scrutiny than those not on the list. For the reporting of ADRs the same rules apply for all medicines. The general requirements for managing products subject to additional monitoring are detailed in *GVP Module X.*

EMA and Member States will maintain and make public a list of medicinal products that are subject to additional monitoring. These medicinal products will be readily identifiable by the introduction of the statement "This medicinal product is subject to additional monitoring" preceded by a standard Inverted black triangle symbol (▼) and followed by an appropriate standardised explanatory statement in their summary of product characteristics (SmPC) and package leaflets (PIL). This explanatory statement will encourage healthcare professionals and patients to report all suspected adverse reactions. Standard texts (QRD Templates) are expected to be finalised in **2nd quarter of 2013.**

The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and to increase awareness about the safe and effective use of certain medicinal products. It is important to emphasize, however, that this concept does not lead to earlier granting of a marketing authorisation.

The list will contain (mandatory scope),

1. medicinal products authorised in the EU that contain a new active substance which, **on 1 January 2011**, was not contained in any medicinal product authorised in the EU, and,
2. any biological medicinal product not covered by the previous category and authorised **after 1 January 2011.**

There is also the possibility (optional scope) to include in the list medicinal products subject to conditions, not falling under the mandatory scope. This can be done at the request of the European Commission or the national competent authority, as appropriate, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC) *[for more details refer to GVP Module X, Chapter X.C].* Additional monitoring status can be assigned to a medicine when it is granted marketing authorisation or at any time during its life cycle.

What changes to the SmPC and PL

As stated above, for medicinal products included on the Additional Monitoring List, the summary of product characteristics (SmPC) and Patients Leaflet (PL) will include the statement: 'This medicinal product is subject to additional monitoring'. This statement will be preceded by the Inverted black triangle symbol (▼) followed by an appropriate standardised explanatory statement in their summary of product characteristics (SmPC) and package

leaflets (PIL). This explanatory statement will encourage healthcare professionals and patients to report all suspected adverse reactions.

For all medicinal products, a standardised text will be included in the PL, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system. Standard texts (QRD Templates) are expected to be finalised in **2nd quarter of 2013.**

Obligations of Marketing Authorisation Holders (MAH)

Marketing authorisation holders should:

- include in the SmPC and PL of their medicinal products subject to additional monitoring, -the black symbol, -the statement "This medicinal product is subject to additional monitoring", and -the standardised explanatory sentence
- include information on the status of additional monitoring in any material to be distributed to healthcare professionals and patients and should make all efforts to encourage reporting of adverse reactions, as agreed with national competent authorities.
- provide evidence on the status of any conditions imposed by the national competent authorities or the European Commission
- submit the relevant variation to include/remove the black symbol, the statement, and the standardised explanatory sentence from the SmPC and PL, where applicable.

How to update product information with regard to the implementation of the black symbol and the statements on additional monitoring and ADR reporting?

The statements on additional monitoring and ADR reporting will be introduced in the next update of the QRD templates. Adaptations to the updated QRD templates may generally be applied for without a separate variation in the course of another variation application of type IB or type II of the "C" category of the Classification Guideline affecting the product information (*see Q/A variations 3.16, and Product information Q19*), so that the necessary update of the product information with regard to the new pharmacovigilance legislation can be introduced without a separate variation application.

For the products that are not under additional monitoring, it is recommended to implement the statements on the ADR reporting as soon as possible, but not later than 2 years **(July 2015)** following the publication date of the next update of the QRD template for medicinal products with regulatory activity and no later than 3 years **(July 2016)** for medicinal products with no regulatory activity.

However, the implementation of these changes may not be delayed for the products under additional monitoring. In case no other variation of the "C" category as mentioned above is submitted within 6 months after the publication of the updated QRD template **(December 2013)**, the implementation of the black symbol and the statements on additional monitoring and ADR reporting has to be introduced by a separate variation application.

Section IX: Reporting of ADRs and Signal Management

(GVP Module VI and Module IX)

Major new changes

Centralised reporting by industry to the Eudravigilance database at the EMA is the major change introduced by the new Directive. However this will only come into effect six months after the Eudravigilance functionality has been updated, audited and approved. This is likely to be sometime in **2015** and until then transitional measures will apply.

Patients reporting: Another major change is the inclusion of reports from patients as valid, reportable ADRs. Also the definition of ADR has been extended to include all reports where harm has occurred to a patient or any reaction that is "noxious and unintended". This will mean that reports of ADRs due to error, misuse, abuse and

where used off-label should also be reported. Only medication errors that result in a serious ADR should be submitted.

For signal management the responsibilities on MAHs are set out in *GVP Module IX*. This essentially sets out the requirement that MAHs should continuously monitor all available data for the identification of potential safety issues. MAHs will also be required to monitor the Eudravigilance database according to their level of access. Signals should follow a process of validation, prioritisation and assessment, and an audit trail of activities should be kept as part of the quality management system. The same criteria for a valid report apply under the new legislation, all reports must have an identifiable patient, reporter, suspect drug and suspect reaction in order to be considered valid. For further guidance on this please refer to the *GVP Module VI.*

Literature reporting: It is intended that at some point in the future the EMA will provide a service for literature reporting for certain products.

Products in Additional Monitoring List: For the reporting of ADRs the same rules apply for all medicines. The general requirements for managing products subject to additional monitoring will be detailed in *GVP Module X.*

Biological products: ICSRs for biologicals and biosimilars should have the batch number and product name. MAHs should follow up for this information if not present in the initial report.

Section X: PV Quality Systems and PV Inspections

(GVP Mod I and GVP Mod III)

PV Quality System is a legal requirement

Marketing authorisation holders (MAH), competent authorities of Member States and EMA should establish and maintain quality assured pharmacovigilance systems. How the systems of these organisations interact while undertaking specific pharmacovigilance processes is described in each respective *Module of GVP*. While there has to be compliance with these legal requirements, the implementation of a quality system should be adapted to the respective organisation.

The definition of a pharmacovigilance system is provided in *Article 1 of Directive 2001/83/EC* as a system used by the marketing authorisation holder and by Member States to fulfill the tasks and responsibilities listed in *Title IX* and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

Guidance on quality systems in *GVP Module I* is consistent with the general principles of the *ISO 9000 Standards* on good quality management practices, specifically the **ISO 9001-2008** Standards on quality management systems.

Inspections of PV Systems

Objectives of a PV Inspection

Pharmaceutical Services inspectors will carry out PV Inspections (risk-based) in order to determine that marketing authorisation holders comply with pharmacovigilance obligations. Such inspections may extend to any firms employed to fulfill marketing authorisation holder's pharmacovigilance obligations (activities described in *Title IX of Directive 2001/83/EC*). In particular, MAHs are required to provide, on request, the pharmacovigilance system master file (PSMF), which will be used to inform inspection conduct.

The new Regulation contains the legal basis for the conduct of pre-authorisation inspections. There is also a clear requirement for an adequate pharmacovigilance system as a condition of marketing authorisation. MA applicants should be aware that the pharmacovigilance system master file may be requested for review during the application process and an inspection may be conducted to establish the adequacy of the (proposed) pharmacovigilance system before authorisation.

For centrally authorised products, the supervisory authority for the conduct of pharmacovigilance inspections is the competent authority of the Member State in which the pharmacovigilance system master file is located.

The objectives of pharmacovigilance inspections are:

- to determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- to identify, record and address non-compliance which may pose a risk to public health;
- to use the inspection results as a basis for enforcement action, where considered necessary.

What a routine PV Inspection may include

Routine pharmacovigilance inspections conducted could include the following elements, as appropriate:

Individual Case Safety Reports (ICSRs):

- collecting, receiving and exchanging reports
- assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality.
- follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
- reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
- record keeping and archiving for ICSRs;

Periodic safety update reports (PSURs), (as applicable):

- completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
- addressing safety topics, providing relevant analyses and actions;
- formatting according to requirements;
- timeliness of submissions;

Ongoing safety evaluation;

- use of all relevant sources of information for signal detection;
- appropriately applied methodology concerning analysis;
- appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
- implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
- timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
- implementation of approved changes to safety communications and product information, including internal distribution and external publication;

Interventional (where appropriate) and non-interventional clinical trials:

- reporting suspected unexpected serious adverse reactions (SUSARs) according to *Directive 2001/20/EC* and non-interventional study cases according to Directive *2001/83/EC;*
- receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
- submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
- appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
- the inclusion of study data in ongoing safety evaluation;

Pharmacovigilance system:

- QPPV roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
- the roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
- accuracy, completeness and maintenance of the pharmacovigilance system master file;
- quality and adequacy of training, qualifications and experience of staff;
- coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- fitness for purpose of computerised systems;
- contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfillment of pharmacovigilance, and are adhered to.

The inspection may include also the system for the fulfillment of conditions of a marketing authorisation and the implementation of risk–minimisation activities, as they relate to any of the above safety topics.

Post inspection procedures and enforcement

The results of an inspection will be provided to the inspected entity that will be given the opportunity to comment on any non-compliance identified. Any non-compliance should also be rectified by the marketing authorisation holder in a timely manner through the implementation of a corrective and preventive action plan. If the outcome of the inspection is that the marketing authorisation holder does not comply with the pharmacovigilance obligations, the Member State concerned shall inform the other Member States, the Agency and the Commission.

Our National Legislation (*Law No. 70(I) of 2001, as amended*) provides for penalties to ensure the enforcement of PV Obligations. Information on the conduct and outcome of pharmacovigilance inspections and the follow-up and evaluation of the consequences may be made publicly available as part of the overall transparency of pharmacovigilance activities. The new legislation re-enforces the cooperation and harmonisation of inspection activities in the EU.

Obligations of MAH

Marketing authorisation holders with authorised products and applicants who have submitted new applications under the centralised procedure are subject to pharmacovigilance inspections. Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

- Always to be inspection-ready as inspections may be unannounced
- To maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the pharmacovigilance system master file
- To ensure that the sites selected for inspection, which may include firms employed by the marketing authorisation holder to perform pharmacovigilance activities, agree to be inspected before the inspection is performed
- To make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection
- To ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified
- To ensure that relevant pharmacovigilance data is accessible from at least one point in the Union
- To ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

Section XI: Web portal and Transparency

Pharmaceutical Services Web Portal

Our web portal is under development and will be made partly publicly available by **April 2013**. The portal will provide to the public and to the health care professionals,

- Detailed Information about the authorised medicines in Cyprus (e.g. composition, dosage form, classifications, MAH, etc.)
- Marketing Authorisation (MA) details about the medicines authorised in Cyprus together with any MA conditions and deadlines (e.g. MA number, date of issue, etc.)
- Product information on authorised medicines (i.e. the Summaries of Product Characteristics and Patient Information Leaflets)
- Information on how to report suspected ADRs (via the Yellow Card Scheme both for healthcare professionals and patients).
- Summaries of Risk Management Plans (RMP) and Public Assessment Reports (PAR) either through the portal or by provision of links to the relative portals of Member-States or to the EMA portal.
- Link to the EMA website

Deadlines and Important Dates

DATE	EVENT
1 January 2011	Additional Monitoring List: -Medicinal products authorised in the EU that contain a new active substance which, **on 1 January 2011**, was not contained in any medicinal product authorised in the EU, and, -Any biological medicinal product not covered by the previous category and authorised **after 1 January 2011.**
21 July 2012	Directive2010/84/EC came into force on **21/7/2012**
21 July 2012	For those MAs granted **before 21 July 2012** without an existing RMP, there is no obligation to submit a RMP unless there are concerns about the risks
10 January 2013	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
30 April 2013	The submission of updated RMP will be enforceable by the Drugs Council. Until the **end of April 2013** new applications without prior update of the RMP will be accepted. The MAH should commit to submit the appropriate variations within an agreed period.
30 April 2013	Pharmaceutical Services portal will be made publicly available (partly)
30 June 2013.	Standard texts (QRD Templates) are expected to be finalised in **2nd quarter of 2013.**
31 December 2013	**Product Information (SmPC, PL)** – The implementation of statements on the ADR reporting may not be delayed for the products under additional monitoring. In case no other variation of the "C" category as mentioned above is submitted within 6 months after the publication of the updated QRD template **(December 2013)**, the implementation of the black symbol and the statements on additional monitoring and ADR reporting has to be introduced by a separate variation application
21 July 2015.	The latest date that MAHs should introduce 'PSMF Summary' in their MAs is the **21st of July 2015**
31 July 2015 **31 July 2016**	**Product Information (SmPC, PL)**-For the products that are not under additional monitoring, it is recommended to implement the statements on the ADR reporting as soon as possible, but not later than 2 years **(July 2015)** following the publication date of the next update of the QRD template for medicinal products with regulatory activity and no later than 3 years **(July 2016)** for medicinal products with no regulatory activity.
December 2015	**Centralised reporting** by industry to the Eudravigilance database at the EMA is the major change introduced by the new Directive. However this will only come into effect six months after the Eudravigilance functionality has been updated, audited and approved. This is likely to be sometime in **2015** and until then transitional measures will apply.

ACRONYMS

ADR	*Adverse Drug Reaction*
DDPS	*Detailed Description of Pharmacovigilance System*
DIR	*Directive*
DSUR	Development Safety Dpdate Report
EC	*European Commission*
EEA	*European Economic Area*
EMA	*European Medicines Agency*
EURD List	*European Union Reference Date List*
GVP	*Good Vigilance Practice*
ICH	*Intrernational Conference on Harmonisation*
ICSR	*Individual Case Safety Report*
IR	*Implementing Regulation*
MA	*Marketing Authorisation*
MAH	*Marketing Authorisation Holder*
NtA WG	*Notice to Applicants Working Group*
PAR	*Public Assessment Report*
PASS	*Post Authorisation Safety Study*
PBRER	*Periodic Benefit-Risk Evaluation Report*
PL (PIL)	*Patient (Information) Leaflet*
PRAC	*Pharmacovigilance Risk Assessment Committee*
PSMF	*Pharmacovigilance Site Master File*
PSUR	*Periodic Safety Update Report*
PV	*Pharmacovigilance*
QS	*Quality System*
RMP	*Risk Management Plan*
RMS	*Risk Management System*
SmPC	*Summary of Products Characteristic*

George Antoniou
Registrar Drugs Council
Pharmaceutical services, MOH, Nicosia
March 2013