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Guideline on good pharmacovigilance practices (GVP)

Module II – Pharmacovigilance system master file (Rev 2)

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*Note: Revision 2 contains the following:

- deletion of text in II.A. referring to transition period as this is not applicable anymore;
- clarification in II.B. that the content of the PSMF should reflect global availability of safety information for medicinal products authorised in the EU, presenting information on the pharmacovigilance system applied at global, regional and local levels;
- deletion of text in II.A. not applicable anymore and rearrangement of sections in II.B.2.1., II.B.2.2., II.B.2.3. and II.C.1.1. to put emphasis on requirements for the submission of the summary of the applicant's pharmacovigilance system at the moment of the initial marketing authorisation application, the requirement for the initial electronic submission of QPPV / contact details and PSMF location information via the Article 57 database (PSMF location registration) and updates to the Article 57 database only, without the need to submit a type IAIN variation (QPPV and PSMF location information maintenance);
- clarification in II.B.4.7. on the inclusion of corrective and preventative action plan(s) that have not yet been agreed for a particular audit or finding in the note required in the PSMF, in order to address queries received from the public;
- addition in II.B.4.8. of the legal reference on the information to be included in the product list regarding the marketing status of the medicinal product.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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This revision of the Module was not subject to public consultation because it concerns only updates and clarifications without changes to the content.

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II.A. Introduction

The legal requirement for marketing authorisation holders to maintain and make available upon request a pharmacovigilance system master file (PSMF) was introduced by Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC (see Recitals (7) and (35), Article 23(4), Article 104(3)(b) of Directive 2010/84/EU) and Regulation (EU) No 1235/2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 (see Recitals (22) and (25), Article 16(3a) of Regulation (EU) No 1235/2010), to harmonise and strengthen the conduct of pharmacovigilance activities in the EU.

The PSMF definition is provided in Article 1(28e) of Directive 2001/83/EC and the minimum requirements for its content and maintenance are set out in the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in this GVP Module.

Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 are hereinafter referred to as REG, DIR and IR, respectively.

The PSMF shall be located 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 [IR Art 7(1)].

It is a requirement of the marketing authorisation application that summary information about the pharmacovigilance system is submitted to the competent authorities [DIR Art 8(3)(ia)]. This summary includes information on the location of the PSMF (see [II.B.2.1.](#)).

This Module provides detailed guidance regarding the requirements for the PSMF, including its maintenance, content and associated submissions to competent authorities.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

II.B. Structures and processes

The PSMF is a legal requirement in the EU. This guidance concerns the requirements for the PSMF and is applicable for any medicinal product authorised in the EU, irrespective of the marketing authorisation procedure. The required content and management of the PSMF applies irrespective of the organisational structure of a marketing authorisation holder, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV's) residence, the location at which he/she carries out his/her tasks and the PSMF location must be within the EU. Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein.

The content of the PSMF should reflect global availability of safety information for medicinal products authorised in the EU, presenting information on the pharmacovigilance system applied at global, regional and local levels.

II.B.1. Objectives

The PSMF shall describe the pharmacovigilance system and support/document its compliance with the requirements. As well as fulfilling the requirements for a PSMF laid down in the legislation and

guidance, it shall also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorisations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by national competent authorities. The PSMF provides an overview of the pharmacovigilance system, which may be requested and assessed by national competent authorities during marketing authorisation application(s) or post-authorisation.

Through the production and maintenance of the PSMF, the marketing authorisation holder and the QPPV should be able to:

- gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
- confirm aspects of compliance in relation to the system;
- obtain information about deficiencies in the system, or non-compliance with the requirements;
- obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

The use of this information should contribute to the appropriate management of and improvement(s) to the pharmacovigilance system.

The requirements for submission of a summary of the marketing authorisation holder's pharmacovigilance system, provision of the content of PSMF and the history of changes to the relevant authority(ies) should enable the appropriate co-ordination of inspections by the Agency, and the planning and effective conduct of inspections by national competent authorities, based on a risk assessment approach.

Responsibilities, in terms of the PSMF, for marketing authorisation holders and applicants, national competent authorities and the Agency are described in detail in Section C (see **II.C.1.**).

II.B.2. Registration and maintenance

II.B.2.1. Summary of the applicant's pharmacovigilance system

Article 8(3)(ia) of Directive 2001/83/EC requires a summary of the applicant's pharmacovigilance system to be included in the marketing authorisation application, which shall include the following elements in module 1.8.1 of the dossier:

- 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;
- a reference to the location where the PSMF for the medicinal product is kept.

Applicants for, and holders of simplified registrations of traditional herbal medicinal products are not required to submit a pharmacovigilance system summary, however, they are required to operate a pharmacovigilance system and prepare, maintain and make available on request a PSMF [based on DIR Art 16g(1)].

For other herbal medicinal products, not falling within the scope of the traditional-use registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system apply.

For homeopathic medicinal products registered via the simplified registration procedure the requirements to operate a pharmacovigilance system, to maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system do not apply [DIR Art 16(3)].

For other homeopathic medicinal products, not falling within the scope of the simplified registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system apply [DIR Art 16(3)].

II.B.2.2. Location, registration and maintenance

The PSMF shall be located within the EU, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)], irrespective of the format (paper-based or electronic format file). Following European Economic Area (EEA) agreements, the PSMF may also be located in Norway, Iceland or Liechtenstein.

At the time of marketing authorisation application, the applicant should submit electronically the PSMF location information using the agreed format [IR Art 26 1(a)], and subsequently include in the application, the PSMF reference number, which is the unique code assigned by the EudraVigilance (EV) system to the master file when the EudraVigilance Medicinal Product Report Message (XEVPRM) is processed (see ¹). Further to the granting of a marketing authorisation, the PSMF will be linked by the marketing authorisation holder to the EVMPD product code(s). All PSMFs must be registered in the Article 57 database.

Marketing authorisation holders shall continue to ensure that their entries in the Article 57 database for medicinal products for human use are up-to-date, including the information about the qualified person responsible for pharmacovigilance (QPPV), name and contact details (telephone and fax numbers, postal address and email addresses) and PSMF location information [based on IR Art 4(4)]. Upon a change in the QPPV or location of the PSMF information, the Article 57 database shall be updated by the marketing authorisation holder immediately and no later than 30 calendar days, in order to have the information in the Article 57 database and on the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 updated and to allow continuous supervision by the competent authorities [based on IR Art 4(4), REG Art 57(2)(c)] (see ²).

The required location information for the PSMF is a physical office address of the marketing authorisation holder or a contracted third party. Where the PSMF is held in electronic form, the location stated must be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location [IR Art 7(3)].

When determining the main site of pharmacovigilance activity, the marketing authorisation holder should consider the most relevant EU site for the pharmacovigilance system as a whole, since the relative importance of particular activities may vary according to products and fluctuate in the short term. The marketing authorisation holder should have an appropriate rationale for the location decision. In the situation where the main activities take place outside the EU, or where a main site cannot be determined, the location should default to the site where the QPPV operates.

¹ ema.europa.eu, Data submission on medicines (Article 57) webpage

² ema.europa.eu, EudraVigilance webpage

II.B.2.3. Transfers of responsibilities for the pharmacovigilance system master file

The pharmacovigilance system may change with time. Transfer or delegation of responsibilities and activities concerning the master file should be documented (see II.B.4.2. and II.B.4.8.) and managed to ensure that the marketing authorisation holder fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the PSMF should also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the QPPV are:

- Updates to the PSMF or its location that are notified to the competent authorities;
- The addition of corrective and/or preventative actions to the PSMF (e.g. following audits and inspections). The QPPV should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;
- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the PSMF to competent authorities;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies or the addition of territories.

Any recipient QPPV should explicitly accept the following changes in writing:

- Transfer of responsibility for a pharmacovigilance system to a QPPV.

The QPPV should be in a position to ensure and to verify that the information contained in the PSMF is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see GVP Module I).

II.B.3. The representation of pharmacovigilance systems

The PSMF, as per definition in Article 1(28e) of Directive 2001/83/EC, shall describe the pharmacovigilance system for one or more medicinal products of the marketing authorisation holder. For different categories of medicinal products the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate PSMF. Those files shall cumulatively cover all medicinal products of the marketing authorisation holder for which a marketing authorisation has been issued in accordance with Directive 2001/83/EC or an authorisation has been granted in accordance with Regulation (EC) No 726/2004.

- It is anticipated that there will be circumstances where a single marketing authorisation holder may establish more than one pharmacovigilance system e.g. specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one marketing authorisation holder. In either case, a single and specific PSMF shall be in place to describe each system.
- In accordance with Articles 8 and 104 of Directive 2001/83/EC, a single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

- Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible ensuring that a PSMF exists to describe the pharmacovigilance system applicable for his products. For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the PSMF of the marketing authorisation holder may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the authorities. The marketing authorisation holder should be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the PSMF in a current and accessible state can be delegated.
- Where applicable, a list of all PSMFs held by the same marketing authorisation holder shall be provided in the annex (see **II.B.4.8.**) [IR Art 3(7)]; this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).
- Submission of summary information to competent authorities cannot contain multiple locations for a single PSMF. The address of the location of the PSMF provided to fulfil the requirement of Article 8(3) of Directive 2001/83/EC (and within the Article 57 database) should be an office address which reflects either the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or the site where the qualified person responsible for pharmacovigilance operates. This address may be different to that of the applicant/marketing authorisation holder, for example, a different office of the marketing authorisation holder or when a third party undertakes the main activities.
- Similarly, the QPPV details aligned to a product in the Article 57 database may be those of a contract QPPV responsible for the pharmacovigilance system for a particular medicinal product, and not necessarily a QPPV directly employed by the marketing authorisation holder.
- When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to competent authorities upon request [IR Art 6]. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place [based on IR Art 6].
- When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs. Accessibility of the PSMF to all the applicable marketing authorisation holder(s), and its provision to competent authorities should be defined in written agreements. It is vital that marketing authorisation holder(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

II.B.4. Information to be contained in the pharmacovigilance system master file

The PSMF shall contain at least all of the documents listed in Article 2 of Commission Implementing Regulation (EU) No 520/2012.

The PSMF shall include documents to describe the pharmacovigilance system. The content of the PSMF 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 following sections and the annex headings described in II.B.6.1. The main principle for the structure of the content of the PSMF 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. The control associated with change of content is described in section II.B.5..

It is accepted that, where no marketing authorisation (and master file) previously existed in the EU, there may be information that cannot be initially provided, for example, compliance information, however, descriptions of what will be implemented should be provided instead.

II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV)

For the QPPV, contact details shall be provided in the marketing authorisation application [DIR Art 8(3)(ia)] and/or via the Article 57 database.

The information relating to the QPPV provided in the PSMF [IR Art 2(1)] shall include:

- a description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
- a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including proof of registration with the EudraVigilance database;
- contact details;
- details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and
- responsibilities of the contact person for pharmacovigilance issues where such a person has been nominated at national level in accordance with Article 104(4) of Directive 2001/83/EC, including contact details.

A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes (see II.B.4.8.). This should outline the activities that are delegated and to whom, and include the access to a medically qualified person if applicable (GVP Module I and [IR Art 10(1)]). This list may be supplied as a copy of a written procedural document provided the required content is covered.

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration with EudraVigilance). The contact details supplied should include name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

II.B.4.2. PSMF section on the organisational structure of the marketing authorisation holder

A description of the organisational structure of the marketing authorisation holder relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between

organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the PSMF shall describe:

- The organisational structure of the marketing authorisation holder(s), showing the position of the QPPV in the organisation.
- The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to product particulars [IR Art 2(2)].

Diagrams may be particularly useful; the name of the department or third party should be indicated.

Delegated activities

The PSMF, where applicable, shall contain a description of the activities and/or services subcontracted by the marketing authorisation holder [IR Art 2 (6)] relating to the fulfilment of pharmacovigilance obligations. This includes arrangements with other parties in any country, Worldwide and if applicable, to the pharmacovigilance system applied to products authorised in the EU.

Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. The list should be organised according to: service providers (e.g. medical information, auditors, patient support programme providers, study data management, etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.). Individual contractual agreements shall be made available at the request of national competent authorities and the Agency or during inspection and audit and the list provided in the Annexes (see II.B.4.8.).

II.B.4.3. PSMF section on the sources of safety data

The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorised in the EU. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the PSMF. Information about third parties (licence partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements (see II.B.4.2. and II.B.4.8.).

Flow diagrams indicating the main stages, timeframes and parties involved may be used. However represented, the description of the process for ICSRs from collection to reporting to competent authorities should indicate the departments and/or third parties involved.

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorisation holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight. In the interests of harmonisation, it is recommended that the list should be comprehensive for products authorised in the EU, irrespective of indication, product presentation or route of administration. The list should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and

non-interventional studies and should be organised per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

II.B.4.4. PSMF section on computerised systems and databases

The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the PSMF [IR Art 2(3)].

Where multiple computerised systems/databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerisation within the pharmacovigilance system can be understood. The validation status of key aspects of computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described. For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

II.B.4.5. PSMF section on pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. **GVP Module I** describes the required minimum set of written procedures for pharmacovigilance. A description of the procedural documentation available (standard operating procedures, manuals, at a global and/or National level etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the PSMF.

A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects shall be included in the PSMF:

- Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc;
- Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PSUR scheduling, production and submission, if applicable (see **GVP Module VII**);
- Communication of safety concerns to consumers, healthcare professionals and the competent authorities;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications [based on IR Art 2(4)].

In each area, the marketing authorisation holder should be able to provide evidence of a system that supports appropriate and timely decision making and action.

The description must be accompanied by the list of processes referred to in Article 11(1) of Commission Implementing Regulation (EU) No 520/2012 under the topic compliance management, as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to competent authority requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this should be indicated (and the names of the applicable countries provided).

II.B.4.6. PSMF section on pharmacovigilance system performance

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the monitoring methods applied and contain as a minimum:

- An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by competent authorities regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timeliness of PSUR reporting to competent authorities in the EU (the annex should reflect the latest figures used by the marketing authorisation holder to assess compliance);
- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in the Annex to the PSMF [IR Art 3(6) and Art 9], alongside the results of (actual) performance measurements.

II.B.4.7. PSMF section on quality system

A description of the quality management system should be provided, in terms of the structure of the organisation and the application of the quality to pharmacovigilance. This shall include:

Document and Record Control

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents (see also **GVP Module I**).

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.
- Information about the documentation systems applied to relevant procedural documents under the control of third parties.

A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided [IR Art 2(5)(a)] and the detailed guidance for the inclusion of these is in section II.B.4.5.

Training

- A description of the resource management for the performance of pharmacovigilance activities:
 - the organisational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational structure (see II.B.4.3.)
- Information about sites where the personnel are located (this is described under sections II.B.4.2. and II.B.4.3.) whereby the sites are provided in the PSMF in relation to the organisation of specific pharmacovigilance activities and in the Annexes which provide the list of site contacts for sources of safety data. However, a description should be provided in order to explain the training organisation in relation to the personnel and site information;
- A summary description of the training concept, including a reference to the location training files.

Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to II.B.4.8. [IR Art 3(5)]. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the Directive 2001/83/EC, and cover a rolling 5 year period.

The PSMF shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the EU criteria for major or critical findings must be indicated (see GVP Module IV). The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In case corrective and preventative action plan(s) have not yet been agreed for a particular audit or finding, the PSMF should include the note required and stating that "corrective and preventative action plan(s) are to be agreed". In the annex, in the list of audits conducted, those associated with unresolved notes in the PSMF, should be identified. The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative

action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved [IR Art 4(3)]. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

II.B.4.8. Annex to the PSMF

An annex to the PSMF shall contain the following documents:

- A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s), and the Member State(s) in which the authorisation is valid [IR Art 3];

The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation:

- the type of procedure for authorisation and procedure number (e.g. centrally authorised, nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure);
- the Rapporteur country or Reference Member State;
- the presence on the market in the EU [DIR Art 23(a), REG Art 13(4)];
- other (non EU) territories where the product is authorised or on the market.

The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity, referral under Article 31 of Directive 2001/83/EC, or included in the list described in Article 23 of Regulation (EC) No 726/2004). The monitoring information may be provided as a secondary list.

For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs.

Where pharmacovigilance systems are shared, all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organised per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the purpose of complying with Article 11(1) of Commission Implementing Regulation (EU) 520/2012 [IR Art 3(2)];
- A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned in accordance with Article 6(2) of Commission Implementing Regulation (EU) No 520/2012 (see **II.B.4.3.**) [IR Art 3(3)];

- A list of tasks that have been delegated by the qualified person for pharmacovigilance [IR Art 3(4)];
- A list of all completed audits, for a period of five years, and a list of audit schedules [IR Art 3(5)];
- Where applicable, a list of performance indicators in accordance with Article 9 of Commission Implementing Regulation (EU) No 520/2012 [IR Art 3(6)];
- Where applicable, a list of other PSMFs held by the same marketing authorisation holder [IR Art 3(7)];

This list should include the PSMF number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not a marketing authorisation holder, the name of the service provider should also be included.

- A logbook in accordance with Article 5(4) of Commission Implementing Regulation (EU) No 520/2012 [IR Art 3(8)]. Other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change [IR Art 5(4)].

II.B.5 Change control, logbook, versions and archiving

It is necessary for marketing authorisation holders to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the PSMF accordingly. The competent authorities may solicit information about important changes to the pharmacovigilance system, such as, but not limited to:

- Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
- Organisational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of PSMF management.

In addition to these changes being documented in the PSMF for the purpose of change control (in the logbook), the QPPV should always been kept informed of these changes.

Changes to the PSMF should be recorded, such that a history of changes is available (specifying the date and the nature of the change), changes to the PSMF must be recorded in the logbook described in Article 5(4) of Commission Implementing Regulation No 520/2012. Descriptive changes to the content of the master file must be recorded in the logbook.

Change history for the information contained in the Annexes may be 'on demand', in which case the logbook would indicate the date of the revision of PSMF content and/or Annex update(s), the history of changes for Annex content would also be updated. Information that is being regularly updated and is contained in the Annexes, such as product and standard operating procedure lists or compliance figures, may include outputs from controlled systems (such as electronic document management systems or regulatory databases). The superseded versions of such content may be managed outside of the PSMF content itself, provided that the history of changes is maintained and available to competent authorities and the Agency on request. If the PSMF has not been requested, or has remained unchanged for a period of time (for example, if the changes in the content of Annexes are

managed outside of the PSMF), it is recommended that a review is conducted periodically. Marketing authorisation holders need to ensure that the obligations concerning the timely provision of the PSMF can be met. It is also noted that the QPPV must be able to gain access to current and accurate information about the pharmacovigilance system, hence permanent access to the PSMF must be enabled, including the information contained in the Annexes (either via the pharmacovigilance master file itself or via access to the systems used to generate the Annex content).

Marketing authorisation holders should be able to justify their approach and have document control procedures in place to govern the maintenance of the PSMF. As a basis for audit and inspections, the PSMF provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

Changes to the PSMF should also account for shared pharmacovigilance systems and delegated activities. A record of the date and nature of notifications of the changes made available to the competent authorities, the QPPV and relevant third parties should be kept in order to ensure that change control is fully implemented.

The PSMF should be retained in a manner that ensures its legibility and accessibility [IR Art 5 and Art 7].

II.B.6. Pharmacovigilance system master file presentation

The PSMF shall be continuously accessible to the QPPV [IR Art 7(2)] and to the competent authorities on request [REG Art 16(3a), DIR Art 23(4), IR Art 7]. The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements [IR Art 4(1)]. Although provision of the document within 7 days of request by a competent authority is stated in Article 23(4) of Directive 2001/83/EC, marketing authorisation holders should be aware that immediate access to the PSMF may also be required by the competent authorities, at the stated PSMF location or QPPV site (if different).

II.B.6.1. Format and layout

The PSMF may be in electronic form on condition that a clearly arranged printed copy can be made available to competent authorities if requested [IR Art 5(3)]. In any format, the PSMF should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

The PSMF should be written in English (unless the marketing authorisation holder only holds approvals in one Member State when it can be written in the EU official language for that territory), indexed in a manner consistent with the headings described in this Module [IR Art 5(2)], and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

The documents and particulars of the PSMF shall be presented with the following headings and, if hardcopy, in the order outlined:

Cover Page to include:

- The unique number assigned by the EV System to the PSMF when the XEVPRM is processed in the XEVMPD (Article 57 database).
- The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system).
- The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system).
- The date of preparation / last update.

The headings used in II.B.4. should be used for the main content of the PSMF. The minimum required content of the Annexes is outlined in II.B.4.8., and additional information may be included in the Annexes, provided that the requirements for the content of the main sections (II.B.1.-7.) are also met. The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

The qualified person responsible for pharmacovigilance, Annex A

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document
- The curriculum vitae of the QPPV and associated documents
- Contact details supplementary to those contained in Article 57 database, if appropriate

The Organisational Structure of the MAH, Annex B

- The lists of contracts and agreements

Sources of safety data, Annex C

- Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

Computerised systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

- Lists of procedural documents

Pharmacovigilance System Performance, Annex F

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules
- List of audits conducted and completed

Products, Annex H

- List(s) of products covered by the pharmacovigilance system
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself.

Documentation to support notifications and signatures concerning the PSMF, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerised systems and databases is used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the PSMF are assured that missing content is intended.

II.C. Operation of the EU network

II.C.1. Responsibilities

II.C.1.1. Marketing authorisation holders and applicants

Marketing authorisation holders shall have a pharmacovigilance system in place to ensure the monitoring and supervision of one or more medicinal products. They are also responsible for introducing and maintaining a PSMF that records the pharmacovigilance system in place with regard to one or more authorised products [DIR Art 23(4), Art 104(3)(b), REG Art 16(3a)]. In accordance with Articles 8(3)(ia) and 104(3) of Directive 2001/83/EC a single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

Applicants are required, at the time of initial marketing authorisation application, to have in place a summary of the pharmacovigilance system that records the system that will be in place and functioning at the time of granting 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 PSMF for review.

The applicant/marketing authorisation holder is responsible for establishing the PSMF in an EU country (at any marketing authorisation holder or contractual partner site including the site of a contractor or marketing partner) and for registering the master file location with the competent authorities in the marketing authorisation application (as applicable) and in the Article 57 database. The PSMF 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 creation, maintenance in a current and accessible state (permanently available for audit and inspection purposes) and provision to competent authorities can be outsourced to a third party, but the marketing authorisation holder retains ultimate responsibility for compliance with the legal requirements.

Marketing authorisation holders are responsible for notifying the Agency immediately of any change in the QPPV details and the PSMF location details. The Agency shall update accordingly the EudraVigilance database referred to in Article 24(1) of Regulation (EC) No 726/2004 and, where necessary, the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 [IR Art 4(4)].

II.C.1.2. National competent authorities

The national competent authorities are obliged to supervise the pharmacovigilance systems of marketing authorisation holders [Recital 7 of Directive 2010/84/EU]. As part of this requirement, they will review the summary information about the pharmacovigilance system included in the marketing authorisation application. The full PSMF may be requested at any time, for example, to review the summary of the pharmacovigilance system of an applicant that has not previously held a marketing authorisation in the EU or where specific concerns about the pharmacovigilance system and/or the product safety profile exist, and in preparation for an inspection (see **GVP Module III**). Information concerning changes to the summary information or content of the PSMF will also be used to inform inspection planning and conduct.

For centrally authorised products, the Member State where the master file is located will become the supervisory authority [Recital 22 of Regulation (EU) No 1235/2010, REG Art 18(3)]. For pharmacovigilance systems that include centrally authorised products, as well as nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, national competent authorities will supervise the pharmacovigilance system in co-operation with the supervisory authority and the Agency. For pharmacovigilance systems that do not include centrally authorised products, individual national competent authorities remain responsible for supervision of the pharmacovigilance system and will work together to minimise duplication of effort.

National competent authorities will share information about pharmacovigilance systems and use the information to inform national risk-based inspection programmes. Inspectors from national competent authorities will report non-compliance with the requirements of legislation and guidance, including both non-compliance with the requirements for the PSMF and the pharmacovigilance system (see **GVP Module III**).

II.C.1.3. The European Medicines Agency

For centrally authorised products, the Agency co-ordinates the inspections of marketing authorisation holders or their service providers. Supervision of the pharmacovigilance system is based on the location of the PSMF, with the Member State where the master file is held becoming the supervisory authority [REG Art 18(3)]. The Agency may request the PSMF in order to fulfil its co-ordination role.

The main responsibility of the Agency, in relation to PSMFs, is the maintenance of EU wide databases, dissemination of information and coordination of EU wide activities. To this effect, the Agency, in collaboration with the Member States and the European Commission, is responsible for the set up and maintenance of the European medicines web-portal for the dissemination of information on medicinal products authorised in the EU [REG Art 26]. The Agency will manage the product list described in Article 57 of Regulation (EC) No 726/2004 which provides a practical mechanism for maintaining up-to-date information about the location of the PSMF, the QPPV contact information and the products relevant to the pharmacovigilance system described in the PSMF. The list of the locations in the EU where PSMFs are kept will be made public via the web-portal [REG Art 26(1)(e)].

II.C.2. Accessibility of the pharmacovigilance system master file

The PSMF shall be kept up to date and be permanently available to the QPPV [IR Art 4(1) and Art 7(2)]. It shall also be permanently available for inspection, at the site where it is kept [IR Art 7(3)] (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced.

According to Article 104(3)(b) of Directive 2001/83/EC the marketing authorisation holder shall maintain and make available on request a copy of the PSMF. The marketing authorisation holder must submit the copy 7 days at the latest after receipt of the request from a national competent authority or the Agency. The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.

In the situation where the same PSMF is used by more than one marketing authorisation holder (where a common pharmacovigilance system is used) the concerned PSMF should be accessible to each, as any of the applicable marketing authorisation holders shall be able to provide the file to the competent authorities within 7 days, upon request [DIR Art 23(4), IR Art 7(4)].

The PSMF should not routinely be requested during the assessment of new marketing authorisation applications (i.e. pre-authorisation), but may be requested on an ad hoc basis, particularly if a new pharmacovigilance system is being implemented, or if product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified.

II.C.3. Transparency

Information on the PSMF location should be made available to the public via the European medicines web-portal [REG Art 26(1)(e)] for transparency and communication purposes.