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Guideline on good pharmacovigilance practices (GVP)

Module II – Pharmacovigilance system master file (Rev 1)

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This version is not valid anymore, but kept on the Agency's website for the purpose of public access to historical documents. For the valid version, please refer to the Agency's GVP webpage for the latest revision of this GVP Module.

*Note: Revision 1 contains the following:

- a correction of the text with regard to the requirements for herbal and homeopathic medicinal products in II.B.2.1. on page 5;

- an emphasis on the requirements of IR Art 2 in a first new sentence of II.B.4. on page 8;

- emphasis on legal references to IR Art 3 and IR Art 5(4) in II.3.4.8. on page 14.

See websites for contact details

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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 Directive 2001/83/EC (Recitals (7) and (35), Article 23(4), Article 104(3)(b)) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (Recitals (22) and (25), Article 16(4), to harmonise and strengthen the conduct of pharmacovigilance activities in the EU.

The pharmacovigilance system master file 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 Implementing Regulation is referenced as IR). The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in this Module of the Good Vigilance Practice(s).

The pharmacovigilance system master file 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. This summary includes information on the location of the pharmacovigilance system master file (see II.B.2.1). There is no requirement for variations for changes in the content of the pharmacovigilance system master file.

This Module provides detailed guidance regarding the requirements for the pharmacovigilance system master file, 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.

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 pharmacovigilance system master file is a legal requirement in the EU. This guidance concerns the requirements for the pharmacovigilance system master file and is applicable for any medicinal product authorised in the EU, irrespective of the marketing authorisation procedure. The required content and management of the pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file should reflect global availability of safety information for medicinal products authorised in the EU, with information on the pharmacovigilance system not just confined to local or regional activities.

II.B.1. Objectives

The pharmacovigilance system master file shall describe the pharmacovigilance system and support/document its compliance with the requirements. As well as fulfilling the requirements for a pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file, 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 pharmacovigilance system master file 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 pharmacovigilance system master file, 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 pharmacovigilance system master file for the medicinal product is kept.

The requirement for submission of a detailed description of the pharmacovigilance system (DDPS) with each marketing authorisation application is no longer applicable. For new applications, the summary of the pharmacovigilance system must be included in the application.

As required by Article 16 of Regulation (EC) No 726/2004 and Article 23 of Directive 2001/83/EC, amendments to the particulars or documents referred to in the summary of the applicant's pharmacovigilance system shall be submitted in accordance with Commission Regulation (EC) No 1234/2008 and the associated Guideline.

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 pharmacovigilance system master file.

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 pharmacovigilance system master file 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 pharmacovigilance system master file and to submit a summary of the pharmacovigilance system do not apply.

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 pharmacovigilance system master file and to submit a summary of the pharmacovigilance system apply.

II.B.2.2. Location

The pharmacovigilance system master file 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.

Details about the location of the pharmacovigilance system master file are required to be entered in the extended Eudravigilance Medicinal Product Dictionary (XEVMPD), and any change to the location shall be notified immediately to the Agency in order to have the information in the XEVMPD and on the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 updated.[IR Art 4(4), REG Art 57(2)(c)] (see Eudravigilance guidance and EMA website guidance on electronic submission of information on medicines).The required location information for the PSMF is a physical office address of the marketing authorisation holder or a contracted third party. Where the pharmacovigilance system master file 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.

II.B.2.3. Registration

All pharmacovigilance system master files must be registered in XEVMPD. The MAH shall update the database with the location of the pharmacovigilance system master file for each product, and update the information immediately upon change, as XEVMPD must be correctly populated with the pharmacovigilance system master file location [IR Art 4(4)].

At the time of marketing authorisation application, the applicant should submit electronically the pharmacovigilance system master file location information using the agreed format as referred to in chapter IV, Article 26, paragraph 1(a) of the Commission Implementing Regulation (EU) No 520/2012, and subsequently include in the application, the pharmacovigilance system master file reference number, which is the unique code assigned by the Eudravigilance (EV) system to the master file when the XEVPRM is processed (guidance on electronic submission of information on medicines is published on the EMA website). On grant of a marketing authorisation application, the pharmacovigilance system master file will be linked by the marketing authorisation holder to the EVMPD product code(s).

Submission of information about the location of the pharmacovigilance system master file that occurs at times other than a marketing authorisation application or a renewal application must be submitted in accordance with Commission Regulation (EC) No 1234/2008 and the associated Guideline. In order to facilitate the submission of master file location information for more than one product covered by a single pharmacovigilance system (and therefore with a common pharmacovigilance system master file), the variations can be grouped.

II.B.2.4. 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 pharmacovigilance system master file 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 pharmacovigilance system master file or its location that are notified to the competent authorities;
- The addition of corrective and/or preventative actions to the pharmacovigilance system master file (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 pharmacovigilance system master file 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 pharmacovigilance system master file is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see Module I).

II.B.3. The representation of pharmacovigilance systems

The pharmacovigilance system master file, as per definition in Article 1(28e) of the 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 pharmacovigilance system master file. 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 pharmacovigilance system master file shall be in place to describe each system.
- In accordance with Articles 8 and 104 of the 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 pharmacovigilance system master file.
- Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible ensuring that a pharmacovigilance system master file 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 pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file 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 pharmacovigilance system master file in a current and accessible state can be delegated.
- Where applicable, a list of all pharmacovigilance system master files 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 pharmacovigilance system master file. The address of the location of the pharmacovigilance system master file provided to fulfil the requirement of Article 8(3) of the Directive 2001/83/EC (and within XEVMPD) 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 XEVMPD 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 pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to competent authorities upon request [IR Art 6]. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place [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 pharmacovigilance system master files. Accessibility of the pharmacovigilance system master file 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 pharmacovigilance system master file shall contain at least all of the documents listed in Article 2 of the Commission Implementing Regulation (EU) No 520/2012.

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 following sections and the annex headings described in II.B.6.1. 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. 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 XEVMPD.

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
- information relating to the contact person for pharmacovigilance 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 (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, 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 pharmacovigilance system master file 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 pharmacovigilance system master file, where applicable, shall contain a description of the delegated activities and/or services relating to the fulfillment of pharmacovigilance obligations [IR Art 2 (6)]. This includes arrangements with other parties in any country, Worldwide and if applicable, to the pharmacovigilance system applied to products authorised in the Community.

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 pharmacovigilance system master file. 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 pharmacovigilance system master file [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. 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 pharmacovigilance system master file.

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

- 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 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 [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 the 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 pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file 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 pharmacovigilance system master file [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 pharmacovigilance system master file should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents (see also 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 [IR Art 2(5)(a)] must be provided, 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 pharmacovigilance system master file. 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 pharmacovigilance system master file 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 Module IV). The audit report must be documented within the quality system; in the pharmacovigilance system master file 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 the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, should be identified. The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file shall contain the following documents:

- A list of medicinal products covered by the pharmacovigilance system master file including the name of the medicinal product, the 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;
- 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 the Directive 2001/83/EC, or included in the list described in Article 23 of the 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 pharmacovigilance system master file(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 pharmacovigilance system master files.

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 the Commission Implementing Regulation (EU) 520/2012 [IR Art 3];
- A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned in accordance with Article 6(2) of the Commission Implementing Regulation No 520/2012 (see II.B.4.3.) [IR Art 3];
- A list of tasks that have been delegated by the qualified person for pharmacovigilance [IR Art 3];
- A list of all completed audits, for a period of five years, and a list of audit schedules [IR Art 3];
- Where applicable, a list of performance indicators in accordance with Article 9 of the Commission Implementing Regulation No 520/2012 [IR Art 3];
- Where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder [IR Art 3];

  This list should include the pharmacovigilance system master file 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 the Commission Implementing Regulation No 520/2012 [IR Art 3] and 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 pharmacovigilance system master file 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 pharmacovigilance system master file management.

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

Changes to the pharmacovigilance system master file 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 the 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 pharmacovigilance system master file content itself, provided that the history of changes is maintained and available to competent authorities and the Agency on request. If the pharmacovigilance system master file 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 pharmacovigilance system master file), it is recommended that a review is conducted periodically. Marketing authorisations holders need to ensure that the obligations concerning the timely provision of the pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file. As a basis for audit and inspections, the pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file shall be continuously accessible to the QPPV [IR Art 7(2)] and to the competent authorities on request [REG Art 16(4), 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 the Article 23(4) of Directive 2001/83/EC, marketing authorisation holders should be aware that immediate access to the pharmacovigilance system master file may also be required by the competent authorities, at the stated pharmacovigilance system master file location or QPPV site (if different).

II.B.6.1. Format and layout

The pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file in order to ensure appropriate control over the content and to assign specific responsibilities for the management of pharmacovigilance system master file in terms of change control and archiving.

The pharmacovigilance system master file 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], 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 pharmacovigilance system master file 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 pharmacovigilance system master file when the XEVPRM is processed in the XEVMPD.
- 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 pharmacovigilance system master files 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 pharmacovigilance system master file. 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 XEVMPD, 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 pharmacovigilance system master file, 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 pharmacovigilance system master file 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 pharmacovigilance system master file 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(4)]. In accordance with Articles 8 and 104 of the 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 pharmacovigilance system master file.

Applicants are required, at the time of initial marketing authorisation application, to have in place a description of the pharmacovigilance system that records the system that will be in place and functioning at the time of grant of the marketing authorisation and placing of the product on the market. During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.

The applicant/marketing authorisation holder is responsible for establishing the pharmacovigilance system master file 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 XEVMPD. The pharmacovigilance system master file shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

The pharmacovigilance system master file 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.

When the QPPV and related contact details change or when the location of the pharmacovigilance system master file changes, the marketing authorisation holder is required to submit the appropriate variation application(s) to the national competent authorities or the Agency, as applicable. Marketing authorisation holders will also be responsible for notifying the Agency immediately of any change in the QPPV details and the pharmacovigilance system master file address details so that the Eudravigilance database referred to in Article 24(1) of Regulation (EC) No 726/2004 and when necessary, the European medicines web-portal, are updated accordingly by the Agency [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 [DIR Recital 7]. As part of this requirement, they will review the summary information about the pharmacovigilance system included in the marketing authorisation application. The full pharmacovigilance system master file may be requested at any time, for example, to review the description of a 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 Module III). Information concerning changes to the summary information or content of the pharmacovigilance system master file 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 [REG Recital 22, 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 pharmacovigilance system master file and the pharmacovigilance system (see 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 pharmacovigilance system master file, with the Member State where the master file is held becoming the supervisory authority [REG Art 18(3)]. The Agency may request the pharmacovigilance system master file in order to fulfil its co-ordination role.

The main responsibility of the Agency, in relation to pharmacovigilance system master files, 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 pharmacovigilance system master file, the QPPV contact information and the products relevant to the pharmacovigilance system described in the pharmacovigilance system master file. The list of the locations in the EU where pharmacovigilance system master files 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 pharmacovigilance system master file shall be maintained in a current state and be permanently available to the QPPV [IR Art 4(1) and Art7(2)]. It shall also be permanently available for inspection, at the site where it is kept (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced [IR Art 7(3)].

According to Article 104 (3)(b) of the Directive the marketing authorisation holder shall maintain and make available on request a copy of the pharmacovigilance system master file. 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 pharmacovigilance system master file should be submitted in a readable electronic format or clearly arranged printed copy.

In the situation where the same pharmacovigilance system master file is used by more than one marketing authorisation holder (where a common pharmacovigilance system is used) the concerned pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master file location should be made available to the public via the Agency web-portal [REG Art 26] for transparency and communication purposes.