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Guideline on good pharmacovigilance practices (GVP)

Module I – Pharmacovigilance systems and their quality systems

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I.A. Introduction

This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorisation holders, competent authorities of Member States and the Agency. How the systems of these organisations interact while undertaking specific pharmacovigilance processes is described in each respective Module of GVP.

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

For performing their pharmacovigilance activities, marketing authorisation holders, competent authorities of Member States and the Agency shall establish and use quality systems that are adequate and effective for this performance. The legal requirement for quality systems was introduced by Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced as DIR) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG) to strengthen pharmacovigilance in the EU. The minimum requirements of these quality systems 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).

While there has to be compliance with these legal requirements, the implementation of a quality system should be adapted to the respective organisation.

By following the overall quality objectives in I.B.4. and the guiding principle in I.B.5. to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each medicinal product covered by a quality system.

The guidance on quality systems in this Module is consistent with the general principles of the ISO 9000 Standards on good quality management practices, specifically the ISO 9001-2008 Standards on quality management systems, issued by the International Organization for Standardization (ISO). The general application of quality management to pharmacovigilance systems is described under I.B. and requirements specific to the operation of the EU network in I.C..

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”.

I.B. Structures and processes

I.B.1. Pharmacovigilance system

A pharmacovigilance system is defined as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR Art 1(28d)].

A pharmacovigilance system, like any system, is characterised by its structures, processes and outcomes. For each specific pharmacovigilance process, including its necessary structures, a dedicated Module is included in GVP.

I.B.2. Quality, quality objectives, quality requirements and quality system

For the purpose of GVP, which provides guidance on structures and processes of a pharmacovigilance system, the quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under I.B.4..

Specific quality objectives and quality requirements for the specific structures and processes of the pharmacovigilance systems are provided in each Module of GVP as appropriate.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management [IR Art 8(2)].

I.B.3. Quality cycle

The quality system shall be based on all of the following activities:

- quality planning: establishing structures and planning integrated and consistent processes;
- quality adherence: carrying out tasks and responsibilities in accordance with quality requirements ;
- quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and
- quality improvements: correcting and improving the structures and processes where necessary [IR Art 8(3)].

I.B.4. Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

I.B.5. Principles for good pharmacovigilance practices

With the aim of fulfilling the overall quality objectives in I.B.4., the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.

- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All persons within the organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in I.B.3..
- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

I.B.6. Responsibilities for the quality system within an organisation

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities [IR Art 10(1), Art 14(1)]. Their responsibility should include adherence to the principles defined in I.B.5..

For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:

- ensuring that the organisation documents the quality system as described in I.B.11.;
- ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- ensuring that adequate resources are available and that training is provided (see I.B.7.);
- ensuring that suitable and sufficient premises, facilities and equipment are available (see I.B.8.);
- ensuring adequate compliance management (see I.B.9.);
- ensuring adequate record management (see I.B.10.);
- reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness (see I.B.12.) and introducing corrective and preventive measures where necessary;
- ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organisation;
- identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see I.B.12.).

In relation to the management responsibilities described above, upper management within an organisation should provide leadership through:

- motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation; and
- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

For competent authorities, all persons involved in the procedures and processes of the quality system established for the performance of pharmacovigilance activities shall be responsible for the good functioning of that quality system and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system [IR Art 8(5)].

I.B.7. Training of personnel for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see I.B.6.).

All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training [IR Art 10(3), Art 14(2)]. For marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel [IR Art 10(3)].

The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel [IR Art 10(3), Art 14(2)]. Training plans should be based on training needs assessment and should be subject to monitoring.

The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.), shall be provided by the organisation to their personnel [IR Art 10(4), Art 14(3)].

I.B.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see I.B.4.) and

also be available for business continuity (see I.B.11.3.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies (see Module VI) in their valid versions and to keep the IT systems up-to-date accordingly.

I.B.9. Specific quality system procedures and processes

I.B.9.1. Compliance management by marketing authorisation holders

For the purpose of compliance management, marketing authorisation holders shall have specific quality system procedures and processes in place in order to ensure the following:

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder [IR Art 11(1)(a)] (see Modules IX and XII);
- the scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorisation or associated with occupational exposure [IR Art 11(1)(b)] (see Modules VI, VII, VIII, IX);
- the submission of accurate and verifiable data on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits [IR Art 11(1)(c)] (see Modules VI and IX);
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals [IR Art 11(1)(d)] (see Modules V, VI, VII, VIII and IX);
- effective communication by the marketing authorisation holder with competent authorities, including communication on new or changed risks (see Module XII and XV), the pharmacovigilance system master file (see Module II), risk management systems (see Module V), risk minimisations measures (see Modules V and XVI), periodic safety update reports (see Module VII), corrective and preventive actions (see Modules II, III and IV) and post-authorisation safety studies (see Module VIII) [IR Art 11(1)(e];
- the update of product information by the marketing authorisation holder in the light of scientific knowledge [IR Art 11(1)(f)] (see Module XII);
- appropriate communication of relevant safety information to healthcare professionals and patients (see Module XII and XV) [IR Art 11(1)(g)].

I.B.9.2. Compliance management by competent authorities

For the purpose of compliance management, competent authorities shall establish specific quality system procedures and processes in order to achieve all of the following objectives:

- ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted [IR Art 15(1)(a)];
- ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines [IR Art 15(1)(b)];
- ensuring independence in the performance of pharmacovigilance activities [IR Art 15(1)(c)];

- ensuring effective communication with patients, healthcare professionals, marketing authorisation holders and the general public [IR Art 15(1)(d)];
- conducting inspections, including pre-authorisation inspections [IR Art 15(1)(f)].

Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on medicinal products should be taken in the sole interest of patients' and public health.

I.B.10. Record management

The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information [IR Art 12(1), Art 16(1)].

A record management system shall be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process [IR Art 12(1), Art 16(1)].

The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;
- effective internal and external communication; and
- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports [IR Art 12(1)].

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process (IR Recital 17). As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

The record management system should be described in a record management policy.

I.B.11. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records [IR Art 8(4)].

A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the organisation should define in advance:

- quality objectives specific to their organisations in accordance with the overall quality objectives provided under I.B.4. and the structure- and process-specific quality objectives in accordance with each Module of GVP; and
- methods for monitoring the effectiveness of the pharmacovigilance system (see I.B.12.).

The quality system shall be documented by:

- documents on organisational structures and assignments of tasks to personnel (see I.B.11.1. and I.B.11.2.);
- training plans and records (see I.B.7.) [IR Art 10(3), Art 14(2)];
- instructions for the compliance management processes (see I.B.9.) [IR Art 11(1), Art 15(1)];
- appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.) [IR Art 10(4), Art 14(3)];
- performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)];
- reports of quality audits and follow-up audits, including their dates and results [IR Art 13(2), Art 17(2)].

Training plans and records shall be kept and made available for audit and inspection [IR Art 10(3), Art 14(2)].

It is recommended that the documentation of the quality system also includes:

- the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- a record management policy;
- records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
- records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been

applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

I.B.11.1. Additional quality system documentation by marketing authorisation holders

In addition to the quality system documentation in accordance with I.B.11., marketing authorisation holders shall document:

- their human resource management in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(b)];
- job descriptions defining the duties of the managerial and supervisory staff [IR Art 10(2)];
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff [IR Art 10(2)];
- instructions on critical processes (see I.B.11.3.) in the pharmacovigilance system master file (PSMF) (see Module II); and
- their record management system in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(c)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

For the requirements of documenting the quality system in the pharmacovigilance system master file (PSMF) or its annexes, see Module II.

I.B.11.2. Additional quality system documentation by competent authorities

In addition to the quality system documentation in accordance with I.B.11., the organisational structures and the distribution of tasks and responsibilities shall be clear and, to the extent necessary, accessible [IR Art 14(1)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

Contact points shall be established [IR Art 14(1)], in particular to facilitate interaction between competent authorities, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.

I.B.11.3. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products;
- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and competent authorities.

I.B.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;
- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.

The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)] in relation to the quality requirements. The quality requirements for each pharmacovigilance process are provided in each Module of GVP as appropriate.

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see I.B.11.) at regular intervals, with the frequency and the extent of the reviews to be determined in a

risk-based manner. Pre-defined programmes for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness [IR Art 13(1), Art 17(1)]. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in Module IV. In relation to the pharmacovigilance system of a marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited [IR Art 13(2)]. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder‘s pharmacovigilance system. For competent authorities, the audit report shall be sent to the management responsible for the matters audited [IR Art 17(2)].

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary [IR Art 13(2), Art 17(2)]. Additionally, the competent authorities should have in place arrangements for monitoring the compliance of marketing authorisations holders with legally required pharmacovigilance tasks and responsibilities. They shall further ensure compliance with the legal requirements by means of conducting inspections of marketing authorisation holders [DIR Art 111(1)] (see Module III). Guidance on compliance monitoring for each pharmacovigilance process is provided in each Module of GVP as appropriate.

Requirements and methods for evaluating the effectiveness of actions taken upon medicinal products for the purpose of minimising risks and supporting the safe and effective use of medicines in patients are described in Module XVI.

I.B.13. Preparedness planning for pharmacovigilance in public health emergencies

Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

For preparedness planning in the EU, see I.C.4..

I.C. Operation of the EU network

I.C.1. Overall pharmacovigilance responsibilities of the applicant and marketing authorisation holder in the EU

The marketing authorisation holder in the EU is responsible for the respective pharmacovigilance tasks and responsibilities laid down in Directive 2001/83/EC, Regulation (EC) No 726/2004 and 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 in order to assure responsibility and liability for its authorised medicinal products and to ensure that appropriate action can be taken, when necessary.

For this purpose, the marketing authorisation holder shall operate a pharmacovigilance system [DIR 104(1)] and shall establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities [IR Art 8(1)].

There may be circumstances where a marketing authorisation holder may establish more than one pharmacovigilance system, e.g. specific systems for particular types of products (e.g. vaccines, products available without medical prescription).

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorisation in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorisation holder for all authorised medicinal products (see Module II). The applicant or the marketing authorisation holder is also responsible for developing and maintaining product-specific risk management systems (see Module V).

Guidance on the structures and processes on how the marketing authorisation holder should conduct the pharmacovigilance tasks and responsibilities is provided in the respective GVP Modules.

I.C.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU

As part of the pharmacovigilance system, the marketing authorisation holder shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV) [DIR Art 104(3)(a)].

The marketing authorisation holder shall submit the name and contact details of the QPPV to the competent authorities in Member States and the Agency [DIR Art 104(3) last paragraph]. Changes to this information should be submitted in accordance with Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisation and the Communication from the Commission - Guideline on the Details of the Various Categories of Variations to the Terms of Marketing Authorisations for Medicinal Products for Human Use and Veterinary Medicinal Products[1].

The duties of the QPPV shall be defined in a job description [IR Art 10(2)]. The hierarchical relationship of the QPPV shall be defined in an organisational chart together with those of other managerial and supervisory staff [IR Art 10(2)].

Information relating to the QPPV shall be included in the pharmacovigilance systems master file (PSMF) [IR Art 2(1)] (see Module II).

Each pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one marketing authorisation holder, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder, provided that the QPPV is able to fulfil all obligations.

In addition to the QPPV, competent authorities in Member States are legally provided with the option to request the nomination of a pharmacovigilance contact person at national level reporting to the QPPV. Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. A contact person at national level may also be nominated as the QPPV.

The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder [IR Art 10(2)]. The marketing authorisation holder should therefore ensure that the QPPV has

[1] See Volume 2C of the Rules Governing Medicinal Products in the EU; http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it in accordance with Module II (see I.C.1.3). The authority over the pharmacovigilance system and the PSMF should allow the QPPV to implement changes to the system and to provide input into risk management plans (see Module V) as well as into the preparation of regulatory action in response to emerging safety concerns (see Module XII).

Overall, the marketing authorisation holder should ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed in I.C.1.3.. In order to do this, the marketing authorisation holder should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:

- emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;
- ongoing or completed clinical trials and other studies the marketing authorisation holder is aware of and which may be relevant to the safety of the medicinal products;
- information from sources other than from the specific marketing authorisation holder, e.g. from those with whom the marketing authorisation holder has contractual arrangements; and
- the procedures relevant to pharmacovigilance which the marketing authorisation holder has in place at every level in order to ensure consistency and compliance across the organisation.

The outcome of the regular reviews of the quality system referred to in I.B.6. and I.B.12. and the measures introduced should be communicated by the managerial staff to the QPPV.

Compliance information should be provided to the QPPV on a periodic basis. Such information may also be used to provide assurance to the QPPV that commitments in the framework of risk management plans and post-authorisation safety systems are being adhered to.

The managerial staff should also inform the QPPV of scheduled pharmacovigilance audits. The QPPV should be able to trigger an audit where appropriate. The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit relevant to the pharmacovigilance system the QPPV is responsible for, so that the QPPV can assure that appropriate corrective actions are implemented.

In particular with regard to its adverse reaction database (or other systems to collate adverse reaction reports), the marketing authorisation holder should implement a procedure to ensure that the QPPV is able to obtain information from the database, for example, to respond to urgent requests for information from the competent authorities or the Agency, at any time. If this procedure requires the involvement of other personnel, for example database specialists, then this should be taken into account in the arrangements made by the marketing authorisation holder for supporting the QPPV outside of normal working hours.

When a marketing authorisation holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder, the QPPV should be notified as early as possible in the due diligence process in order that the potential impact on the pharmacovigilance system can be assessed and the system be adapted accordingly. The QPPV may also have a role in determining what pharmacovigilance data should be requested from the other company, either pre- or post-acquisition. In this situation, the QPPV should be made aware of the sections of the contractual arrangements that relate to responsibilities for pharmacovigilance activities and safety data exchange and have the authority to request amendments.

When a marketing authorisation holder intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system, the QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see I.C.1.5.) so that all necessary provisions relevant to the pharmacovigilance system are included.

I.C.1.2. Qualifications of the qualified person responsible for pharmacovigilance in the EU

The marketing authorisation holder shall ensure that the QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities [IR Art 10(1)]. The QPPV should have skills for the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences as well as epidemiology and biostatistics. Where the QPPV has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC, the marketing authorisation holder shall ensure that the QPPV is assisted by a medically trained person (i.e. in accordance with Article 24 of Directive 2005/36/EC) and this assistance shall be duly documented [IR Art 10(1)].

The expectation is that the applicant or marketing authorisation holder will assess the qualification of the QPPV prior to appointment by, for example, reviewing university qualifications, knowledge of EU pharmacovigilance requirements and experience in pharmacovigilance.

The applicant or marketing authorisation holder should provide the QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the medicinal products covered by the pharmacovigilance system.

I.C.1.3. Role of the qualified person responsible for pharmacovigilance in the EU

The qualified person responsible for pharmacovigilance in the EU (QPPV) is a natural[2] person.

The QPPV appointed by the marketing authorisation holder shall be appropriately qualified (see I.C.1.2.) and shall be at the marketing authorisation holder's disposal permanently and continuously (see I.C.1.1.) [DIR Art 104 (3)(a)]. The QPPV shall reside and operate in the EU [DIR Art 104 (3) last paragraph]. Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein. Back-up procedures in the case of absence of the QPPV shall be in place [IR Art 2(1)(d)] and should be accessible through the QPPV's contact details. The QPPV should ensure that the back-up person has all necessary information to fulfil the role.

The QPPV shall be responsible for the establishment and maintenance of the marketing authorisation holder's pharmacovigilance system [DIR Art 104 (3) last paragraph] and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities [IR Art 10(2)] and to promote, maintain and improve compliance with the legal requirements [IR Art 2(1)(a)]. Hence, the QPPV should have access to the pharmacovigilance system master file (PSMF) (see Module II) and be in a position of authority to ensure and to verify that the information contained in the PSMFis an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.

In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV should include:

[2] A natural person is a real human being, as distinguished from a corporation which is often treated at law as a fictitious person.

- having an overview of medicinal product safety profiles and any emerging safety concerns;
- having awareness of any conditions or obligations adopted as part of the marketing authorisations and other commitments relating to safety or the safe use of the products;
- having awareness of risk minimisation measures;
- being aware of and having sufficient authority over the content of risk management plans;
- being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the EU or pursuant to a risk management plan agreed in the EU;
- having awareness of post-authorisation safety studies requested by a competent authority including the results of such studies;
- ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;
- ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the competent authorities in Members States and the Agency;
- ensuring a full and prompt response to any request from the competent authorities in Members States and from the Agency for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product;
- providing any other information relevant to the benefit-risk evaluation to the competent authorities in Members States and the Agency;
- providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);
- acting as a single pharmacovigilance contact point for the competent authorities in Member States and the Agency on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

This responsibility for the pharmacovigilance system means that the QPPV has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance). Specifically for the adverse reaction database, if applicable, the QPPV should be aware of the validation status of the database, including any failures that occurred during validation and the corrective actions that have been taken to address the failures. The QPPV should also be informed of significant changes that are made to the database (e.g. changes that could have an impact on pharmacovigilance activities).

The QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

I.C.1.4. Specific quality system processes of the marketing authorisation holder in the EU

In applying the requirements set out in I.B.9.1. in the EU, the marketing authorisation holder shall put in place the following additional specific quality system processes for ensuring:

- the submission of adverse reaction data to EudraVigilance within the legal timelines [IR Art 11(c)];

- the monitoring of the use of terminology referred to in IR Art 25(1) either systematically or by regular random evaluation [IR Art 25(3)];
- the retention of minimum elements of the pharmacovigilance system master file (PSMF) (see IR Art 2 and Module II) as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the marketing authorisation holder [IR Art 12(2)];
- the retention of pharmacovigilance data and documents relating to individual authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist [IR Art 12(2)];
- that the product information is kept up-to-date by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal an on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal [IR Art 11(1)(g)].

The retention periods above apply unless the documents shall be retained for a longer period where EU or national law so requires [IR Art 12(2)].

During the retention period, retrievability of the documents should be ensured. Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time.

Documents transferred in situations where the business of the marketing authorisation holder is taken over by another organisation should be complete.

I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder

The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties [IR Art 6(1)], i.e. to another organisation or person (where the same requirements apply to a person as for an organisation). This may include the role of the QPPV. The marketing authorisation holder shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 6(1)]. The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorisation holder.

Where a marketing authorisation holder has subcontracted some tasks of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks [IR Art 11(2)]. All guidance provided in GVP is also applicable to the other organisation to which the tasks have been subcontracted.

When subcontracting tasks to another organisation, the marketing authorisation holder shall draw up subcontracts [IR Art 6(2)] and these should be detailed, up-to-date and clearly document the contractual arrangements between the marketing authorisation holder and the other organisation, describing arrangements for delegation and the responsibilities of each party. A description of the subcontracted activities and/or services shall be included in the pharmacovigilance system master file (PSMF) [IR Art 2(6)] and a list of the subcontracts shall be included in an annex to the PSMF, specifying the product(s) and territory(ies) concerned [IR Art 6(2)] (see Module II). The other

organisation may be subject to inspection at the discretion of the competent or supervisory authority in the relevant Member State.

Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the marketing authorisation holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data exchange, together with, for example, agreed definitions, tools, assignments and timelines. The contractual arrangements should also contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases. Further, they should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.

With respect to centrally authorised products, contractual arrangements between different marketing authorisation holders should also be in place in relation to separately authorised medicinal products with the application of Article 82(1) of Regulation (EC) No 726/2004 in order to ensure conduct of pharmacovigilance on the basis of complete worldwide data sets.

For responsibilities of the marketing authorisation holder towards the QPPV in this context, see I.C.1.1..

I.C.2. Overall pharmacovigilance responsibilities within the EU regulatory network

The competent authorities in Member States and the Agency are responsible for the respective pharmacovigilance tasks and responsibilities imposed on them by Directive 2001/83/EC, Regulation (EC) No 726/2004 and 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 in order to ensure that appropriate action can be taken, when necessary.

For this purpose each competent authority in a Member State as well as the Agency shall operate a pharmacovigilance system [DIR 101(1)] and shall establish and use an adequate and effective quality system for performing their pharmacovigilance activities [IR Art 8(1)].

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the EU [REG Art 28e].

The requirement in I.B.11.2. according to which competent authorities shall keep accessible clear descriptions of the organisational structures, assignment of tasks and responsibilities as well as contact points [IR Art 14(1)], should relate to the interaction between competent authorities in Member States, the Agency, the European Commission, marketing authorisation holders and persons reporting information on the risks of medicinal products.

Guidance on the structures and processes to enable the competent authorities in Member States and the Agency to conduct the pharmacovigilance tasks and responsibilities is provided in the respective Modules of GVP.

I.C.2.1. Role of the competent authorities in Member States

Each Member State shall designate a competent authority for the performance of pharmacovigilance [DIR Art 101(3)]. This authority is usually the same as the competent authority responsible for granting national marketing authorisations.

Each competent authority in a Member State must operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in EU pharmacovigilance activities [DIR Art 101(1)]. In this context, the competent authority in a Member State is responsible for the safety monitoring of each medicinal product, independent of its route of authorisation, in the territory of that Member State. In particular, the competent authority in each Member State shall be responsible for monitoring data originating in their territory [IR Art 18(4)].

For nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, the competent authority in a Member State is responsible for granting, varying, suspending and revoking a marketing authorisation. The pharmacovigilance tasks and responsibilities of competent authorities in Member States for each process in relation to such products, are detailed in the respective Modules of GVP.

For products authorised through the mutual recognition or the decentralised procedure, one Member State acts as the Reference Member State. For practical reasons, the competent authority of the Reference Member State should coordinate communication with the marketing authorisation holder on pharmacovigilance matters and monitor the compliance of the marketing authorisation holder with legal pharmacovigilance requirements. These arrangements do not replace the legal responsibilities of the marketing authorisation holder with respect to individual competent authorities and the Agency.

Nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, may become subject to regulatory procedures at EU level on pharmacovigilance grounds. If a Commission Decision for a nationally authorised product exists as an outcome of such a procedure, the competent authorities in Member States are responsible for the implementation of the Commission Decision and also for its follow-up, unless exceptionally further action by the Agency and the European Commission has been foreseen in the Commission Decision reflecting the outcome of the regulatory procedure (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

The pharmacovigilance tasks and responsibilities of competent authorities in Member States in relation to centrally authorised products are also detailed in the respective Modules of GVP. They include the collaboration in signal detection (see Module IX) and implementation of Commission Decisions regarding risk management of centrally authorised products addressed to Member States (see Module V). Where urgent action is essential to protect human health or the environment, the competent authority in a Member State, on its own initiative or at the European Commission's request, may suspend the use of a centrally authorised product in its territory (see Modules XII).

Competent authorities in Member States are responsible for pharmacovigilance inspections of organisations in their territory in relation to medicinal products. This is independent of the route of marketing authorisation as well as which competent authority granted the marketing authorisation for the respective medicinal product (see Module III).

In relation to the various aspects of the role described above, each Member State's competent authority should ensure that all pharmacovigilance data are shared between competent authorities in other Member States, the European Commission and the Agency for each process in accordance with the legislation and the guidance in the respective GVP Modules.

I.C.2.2. Role of the European Commission

The European Commission is the competent authority for medicinal products authorised through the centralised procedure and is responsible for granting, varying, suspending and revoking their marketing authorisations by adoption of Commission Decisions on the basis of Opinions adopted by the Committee for Medicinal Products for Human Use (CHMP) (see I.C.2.3.3.).

Further, the European Commission adopts Commission Decisions in relation to nationally authorised medicinal products subject to regulatory procedures at EU level, including on pharmacovigilance grounds. The European Commission may also initiate such procedures (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

I.C.2.3. Role of the European Medicines Agency

I.C.2.3.1. General role of the Agency and the role of the Agency's secretariat

The role of the Agency is to coordinate the monitoring of medicinal products for human use authorised in the EU and to provide advice on the measures necessary to ensure their safe and effective use, in particular, by coordinating the evaluation and implementation of legal pharmacovigilance requirements and the monitoring of such implementation. The tools established and maintained by the Agency for the coordination are presented in the GVP Modules for each process.

The Agency provides coordination and technical, scientific and administrative support to the Pharmacovigilance Risk Assessment Committee (PRAC) (see I.C.2.3.2.) and the Committee for Medicinal Products for Human Use (CHMP) (see I.C.2.3.3.) and coordination and technical and administrative support to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) (see I.C.2.3.4.), as well as coordination between the committees and the CMDh.

Pharmacovigilance for centrally authorised products is conducted by the Agency with the involvement of the Rapporteurs, the PRAC and the CHMP. The Agency should take the lead for communicating with the marketing authorisation holders of centrally authorised products. The respective responsibilities for each pharmacovigilance process are detailed in the GVP Modules.

For nationally authorised products, the Agency coordinates regulatory procedures at EU level on pharmacovigilance grounds through providing support to the CMDh and CHMP (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

The Agency also cooperates with other EU bodies as necessary.

Specific pharmacovigilance tasks of the Agency include:

- running the EudraVigilance database [REG Art 57(d)];
- monitoring selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances [REG Art 27] (see Module VI);
- running processes for the EU coordination of the assessment of periodic safety update reports (see Module VII) and oversight of post-authorisation safety studies (see Module VIII);
- tasks relating to signal detection [REG Art 28a(1)(c), IR Art 18-24] (see Module IX);
- tracking of follow-up of safety concerns and other pharmacovigilance matters at EU level (see Module XII);

- assisting Member States with the rapid communication of information on safety concerns to healthcare professionals and coordinating the safety announcements of the national competent authorities [REG Art 57(e)] (see Module XV);
- distributing appropriate information on safety concerns to the general public, in particular by setting up and maintaining the European medicines web-portal [REG Art 57(f)] (see Module XV);
- coordination of safety announcements between national competent authorities for active substances contained in medicinal products authorised in more than one Member State, including providing timetables for the publication of information [DIR 106a(3)] (see Module XV);

and specifically in relation to centrally authorised products:

- assessing updates to risk management systems [REG Art 28a(1)(b)] (see Module V);
- monitoring the outcome of risk minimisation measures [REG Art 28a(1)(a)] (see Module XVI).

I.C.2.3.2. Role of the Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for providing recommendations to the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems, including the monitoring of the effectiveness of those risk management systems [REG Art 56(1)(aa)]. The Details on the responsibilities for each process are presented in the respective GVP Modules. The Mandate and Rules of Procedure of the PRAC are published on the Agency's website[3].

I.C.2.3.3. Role of the Committee for Medicinal Products for Human Use (CHMP)

The Committee for Medicinal Products for Human Use (CHMP) is responsible for evaluating applications and formulating Opinions serving as a basis for granting, varying, suspending or withdrawing marketing authorisations for centrally authorised products. The CHMP also prepares Opinions on safety concerns emerging after a marketing authorisation has been granted for centrally authorised products or, for nationally authorised products, including those through the mutual recognition or the decentralised procedure, in the framework of regulatory procedures at EU level in which at least one centrally authorised product is involved (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons), procedures for the assessment of periodic safety update reports (PSURs) (see Module VII) and procedures for post-authorisation safety studies (see Module VIII). For questions related to pharmacovigilance activities and risk management systems, the CHMP relies on the recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC). The specific responsibilities of each party for each pharmacovigilance process are described in the GVP Modules. The Rules of Procedure of the CHMP are published on the Agency's website[4].

I.C.2.3.4. Role of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)

The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) is responsible for examining any question relating to marketing authorisations for medicinal products authorised through the mutual recognition or the decentralised procedure and questions on the

[3] http://www.ema.europa.eu
[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7a

variation of marketing authorisations granted by the Member States as well as questions arising for nationally authorised products from assessments of periodic safety update reports (see Module VII), post-authorisation safety studies (see Module VIII) and during regulatory procedures at EU level. The CMDh shall reach a position, based on a PRAC recommendation, on regulatory procedures at EU level when only nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, are involved [DIR Art 107k](see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons). The responsibilities of the CMDh for each pharmacovigilance process are described in the respective GVP Modules. The Rules of Procedure of the CMDh and the Functions and Tasks for CMDh are published on the HMA website[5].

I.C.2.4. Specific quality system processes of the quality systems of competent authorities in Member States and the Agency

In applying the requirements set out in I.B.9.2. in the EU, the competent authorities in Member States and the Agency shall put in place the following additional specific quality system processes for:

- monitoring and validating the use of terminology referred to in IR Art 25(1), either systematically or by regular random evaluation [IR Art 25(3)];
- assessing and processing pharmacovigilance data in accordance with the timelines provided by legislation [IR Art 15(1)(b)];
- ensuring effective communication within the EU regulatory network in accordance with the provisions on safety announcements in Article 106a of Directive 2001/83/EC [IR Art 15(1)(d)] (see Module XV);
- guarantying that competent authorities in Member States and the Agency inform each other and the European Commission of their intention to make announcements relating to the safety of a medicinal product or an active substance contained in a medicinal product authorised in several Member State (see Modules XII and XV) [IR Art 15(1)(e)];
- arranging for the essential documents describing their pharmacovigilance systems to be kept as long as the system exists and for at least further 5 years after they have been formally terminated [IR Art 16(2)];
- ensuring that pharmacovigilance data and documents relating to individual authorised medicinal products are retained as long as the marketing authorisation exists or for at least further 10 years after the marketing authorisation has expired [IR Art 16(2)].

In this context, documents relating to a medicinal product include documents of a reference medicinal product where this is applicable.

The retention periods above apply unless the documents shall be retained for a longer period where EU or national law so requires [IR Art 16(2)].

During the retention periods referred to above, retrievability of the documents should be ensured.

Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If pharmacovigilance documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time.

[5] http://www.hma.eu/205.html

The legal requirements for record management (see I.B.10.) imply accessibility to the records from within the EU, preferably at a single point.

In addition to the above, competent authorities in Member States shall establish procedures for collecting and recording all suspected adverse reactions that occur in their territory (see Module VI) [IR Art 15(2)].

In addition to the above, the Agency shall establish procedures for literature monitoring in accordance with Article 27 of Regulation (EC) No 726/2004 (see Module VI) [IR Art 15(3)].

In addition to the quality system documentation in accordance with I.B.11. and I.B.11.2., competent authorities in Member States and the Agency shall clearly determine, and to the extent necessary, keep accessible the organisational structures and the distribution of tasks and responsibilities [IR Art 14(1)] as well as establish contact points [IR Art 14(1)], in particular to facilitate interaction between competent authorities in Member States, the Agency, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.

Quality audits of the Member States' and Agency 's pharmacovigilance systems (see I.B.12.) shall be performed according to a common methodology [IR Art 17(1)]. The results of audits shall be reported by competent authorities in Member States in accordance with Article 101(2) of Directive 2001/83/EC and by the Agency in accordance with Article 28f of Regulation (EC) No 726/2004 (see Module IV).

I.C.2.5. Quality system requirements for pharmacovigilance tasks delegated or transferred by competent authorities in Member States

A competent authority in a Member State may delegate any pharmacovigilance task to another Member State subject to a written agreement of the latter Member State [DIR Art 103]. The written agreement should be reflected by exchange of letters, defining the scope of the delegation.

A competent authority in a Member State may transfer any or all of the pharmacovigilance tasks to another organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the competent authority in a Member State.

Where tasks are transferred to another organisation, the competent authority in a Member State should ensure that the tasks are subject to a quality system compliant with the legal requirements applicable to their own organisation.

I.C.2.6. Transparency of the quality system of the EU regulatory network

The European Commission (EC) shall publish every three years a report on the performance of pharmacovigilance based on the reports submitted by the competent authorities in Member States (first EC report due on 21 July 2015) and by the Agency (first EC report due on 2 January 2014) on the results of their regular pharmacovigilance system audits (see Module IV) [DIR Art 101(2), Art 108b, REG Art 28f, Art 29].

I.C.3. Data protection in the EU

All legal requirements of the IR, including those relating to the record management described in I.B.10., shall apply without prejudice to the obligations of national competent authorities and marketing authorisation holders relating to their processing of personal data under Directive 95/46/EC or the obligations of the Agency relating to its processing of personal data under Regulation (EC) No 45/2001 [IR Art 39].

I.C.4. Preparedness planning in the EU for pharmacovigilance in public health emergencies

The pharmacovigilance systems of marketing authorisation holders, competent authorities in Member States and the Agency should be adaptable to public health emergencies. Preparedness plans should be developed as appropriate (see I.B.13.).

A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the Council.

Pharmacovigilance requirements for public health emergencies should be considered by the competent authorities in Member States, the European Commission and the Agency on a case-by-case basis and appropriately notified to marketing authorisation holders and the public. The Agency publishes its notifications on the Agency's website.