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Inspections, Human Medicines Pharmacovigilance & Committees Division

EMA pharmacovigilance system manual

Version 1.2

Revision history

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20/01/2014	F. Diafouka	Adoption	- Insertion of comments received from all 4 Human Medicines divisions.	Adopted by Human Medicines Leadership Team on 20/01/2014
28/01/2014	F. Diafouka	Sign off prior to internal publication	- Sign off of EMA Pharmacovigilance System Manual for internal use	Signed off by the EMA Executive Director on 28/01/2014
12/06/2014	F. Diafouka	Update for sign off prior to publication on EMA website	- Insertion of updated organisational chart - Harmonised description of Divisions' responsibilities - Updated description of EU Telematics programme - Deletion of 3 annexes	Signed off by the EMA Executive Director on 30/06/2014
18/08/2016	A. Segec	Update of EMA organisational structure	- Insertion of updated organisational chart and updated references to Agency organisational and governance entities - Updated description of Divisions' responsibilities - Updated list of pharmacovigilance tasks and Annex 1	Adopted by Medicines Leadership Team on 12/09/2016 and endorsed by the EXB on 29/09/2016 Signed off by the EMA Executive Director on 14/10/2016

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1. Legal background

Legal requirements related to the European Medicines Agency (EMA or the Agency) pharmacovigilance system for human medicines are laid down in Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012.

Article 28e of Regulation (EC) No 726/2004 specifies that "*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 in the Union.*" The establishment of a functioning EMA pharmacovigilance system is to be the subject of regular audits and regular publication of a report by the European Commission, as outlined in Articles 28f and 29 of Regulation (EC) No 726/2004. Article 28f states that "*the Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis*", while Article 29 emphasises that "*the Commission shall make public a report on the performance of the pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter.*"

Article 87a(b) of Regulation (EC) No 726/2004 sets the framework for Commission Implementing Regulation (EU) No 520/2012 by stating that "[i]*n order to harmonise the performance of the pharmacovigilance activities provided for in this Regulation, the Commission shall adopt implementing measures as provided for in Article 108 of Directive 2001/83/EC covering the following areas:*

[…]

(b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency;".

Three paragraphs in Article 8 of Commission Implementing Regulation (EU) No 520/2012 set out the specific characteristics of the EMA pharmacovigilance system. Those characteristics are described further in the non-legally binding good pharmacovigilance practice (GVP) modules I and II, relating respectively to the description of the pharmacovigilance systems and their quality systems for competent authorities and for marketing authorisation holders and the pharmacovigilance system master file for marketing authorisation holders.

Article 8 of Commission Implementing Regulation (EU) No 520/2012 makes reference in particular to the following points:

"*1. Marketing authorisation holders, the national competent authorities and the Agency shall establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.*

2. The quality system shall cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

[…]

5. All persons involved in the procedures and processes of the quality systems established by the national competent authorities and the Agency for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system".

2. EMA mission and principal activities

In accordance with the provisions of European Union (EU) legislation relating to medicinal products, the EMA is the EU body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

The EMA is responsible, in particular, for:

*   providing independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to the promotion and protection of public health that involve medicines;

*   implementing measures for continuously supervising the quality, safety and efficacy of authorised medicines to ensure that their benefits outweigh their risks;

*   publishing impartial and comprehensible information about medicines and their use;

*   developing best practice for medicines evaluation and supervision in Europe, and contributing alongside the Member States and the European Commission to the harmonisation of regulatory standards at the international level.

The mission statement of the EMA can be found on its public website.

The scientific resources and experts dedicated to the performance of pharmacovigilance activities defined by the EU legislation include, in particular, the Pharmacovigilance Risk Assessment Committee (PRAC), together with the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures Human (CMDh).

The mandate of the PRAC covers all aspects of the risk management, including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit. The CHMP is responsible for preparing the Agency's opinions on all questions concerning medicines for human use and plays a key role in the monitoring of the change in the benefit-risk balance for medicinal products, making, when necessary recommendations to the European Commission regarding changes to a medicine's marketing authorisation, or its suspension/withdrawal from the market. The CMDh is responsible for examining any questions relating to marketing authorisations and variations of the terms of the marketing authorisation for medicinal products authorised through the mutual recognition or the decentralised procedure.

In order to comply with its legal obligations related to the promotion and protection of public health through the safety monitoring of authorised medicinal products and to detect and confirm any change to their risk-benefit balance, the Agency operates a quality assured pharmacovigilance system. The EMA has a coordinating role in the functioning of the EU pharmacovigilance system in collaboration with the Member States and the European Commission.

3. EMA pharmacovigilance system

The EMA pharmacovigilance system is described in this manual, which covers the EMA organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management. This manual does not cover pharmacovigilance aspects related to veterinary medicines.

The detailed operational requirements of all EMA pharmacovigilance tasks that constitute the EMA pharmacovigilance system are set out in the Agency's policies, standard operating procedures (SOPs) and work instructions (WINs), which are part of the EMA's integrated quality management system and can be found on the [Agency's website](#).

The EMA pharmacovigilance system is embedded in the Agency's overall quality system, and takes account of key corporate governance structure requirements outlined in the Agency's mission and policies, such as transparency and data protection (see Figure 1.).

Figure 1. The EMA pharmacovigilance system in the context of the EMA quality system
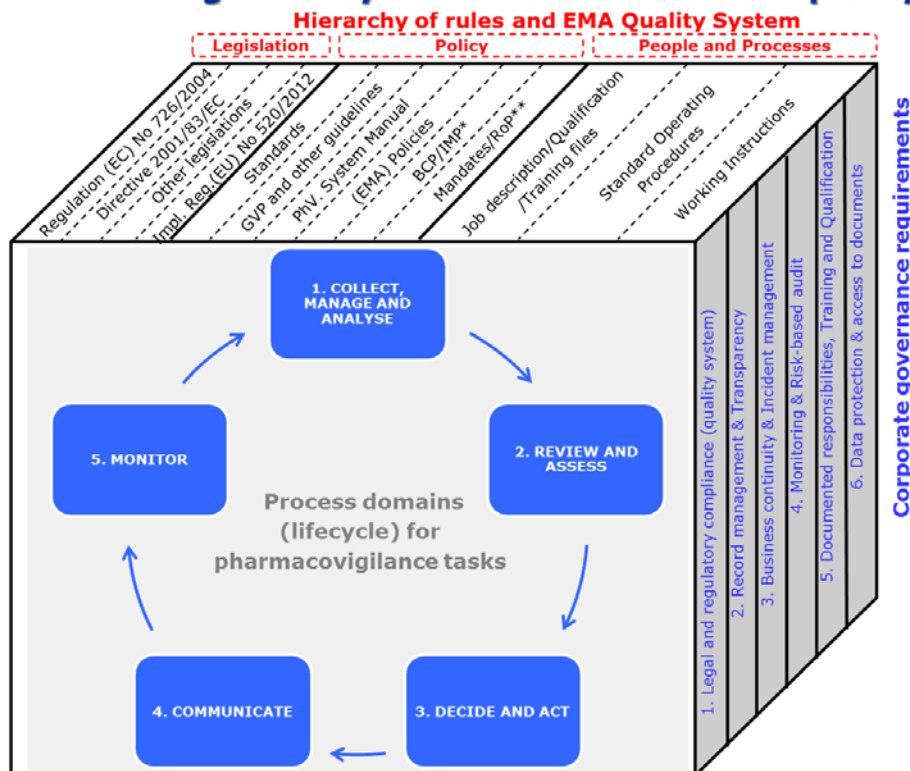
* BCP = Business continuity plan, IMP = incident management plan. ** RoP = rules of procedure.

The pharmacovigilance system manual sets out the key principles for monitoring the performance of the EMA pharmacovigilance system and reporting on the EMA pharmacovigilance tasks, as laid down in the legislation.

3.1. Documentation

The EMA pharmacovigilance system is documented in this pharmacovigilance system manual, which is reviewed at least once a year by the Medicines Leadership Team, which provides recommendations to the EMA Executive Board. Updates of the manual take account of:

- ongoing implementation of the pharmacovigilance legislation leading to the adoption of new pieces of guidance (e.g. GVP) as well as the development and operation of new pharmacovigilance tasks or re-engineering of existing pharmacovigilance tasks;

- ongoing development and implementation of other legislation, as applicable;

- scientific and technical advances;

- relevant EMA organisational changes leading to changes of accountability or responsibility.

The pharmacovigilance system manual and any change to it are authorised by the Executive Director of the EMA.

It is the responsibility of the Inspections, Human Medicines Pharmacovigilance & Committees Division to maintain the pharmacovigilance system manual for which the signed copy is published. The pharmacovigilance system manual is modified by staff appointed by the Head of Division.

For any request for amendment of the EMA pharmacovigilance system manual, the Head of Inspections, Human Medicines Pharmacovigilance & Committees Division or the lead author can be contacted.

If the change request is authorised by the EMA Executive Director further to its agreement by the Medicines Leadership Team and endorsement by the EMA Executive Board, the electronic version (master copy) of the pharmacovigilance system manual will be updated and a change notification will be published on the Agency's intranet and sent both to the initial requester and the Medicines Leadership Team. If the change request is not approved, the initial requester as well as the Medicines Leadership Team will receive a notification, together with a justification for not accepting the change.

3.2. Definition and characteristics

The EMA pharmacovigilance system is the system used to fulfil the Agency's legal tasks and responsibilities in relation to pharmacovigilance, and is designed to monitor the safety of authorised medicinal products within the Agency's scope and detect and confirm any change to their risk-benefit balance. The EMA pharmacovigilance system is characterised by its structures, resources, processes, tools, outputs and outcomes.

The cycle of the quality system is based on the four 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.
- Quality improvements: correcting and improving the structures and processes where necessary.

3.3. EMA data and record management

All data, documents and records related to the EMA pharmacovigilance system are physically and electronically stored in designated folders and databases, and retained in accordance with the relevant legislation and requirements of the EMA integrated quality management system on data and record management.

3.4. Subcontracting of EMA pharmacovigilance tasks

The subcontracting of EMA pharmacovigilance tasks belonging to the EMA pharmacovigilance system is done in accordance with the requirements of the EMA integrated quality management system.

The EMA retains responsibility for the pharmacovigilance tasks that have been subcontracted and performs regular audits of subcontractors.

A list of subcontractors involved in EMA pharmacovigilance tasks is maintained by the Agency.

4. Overall responsibilities

4.1. EMA organisational structure

The EMA organisational chart (see Figure 2.) displays the overall matrix approach, the hierarchical relationship within divisions and the relationships between all EMA divisions.

Figure 2. EMA organisation chart (as of 1st September 2016)
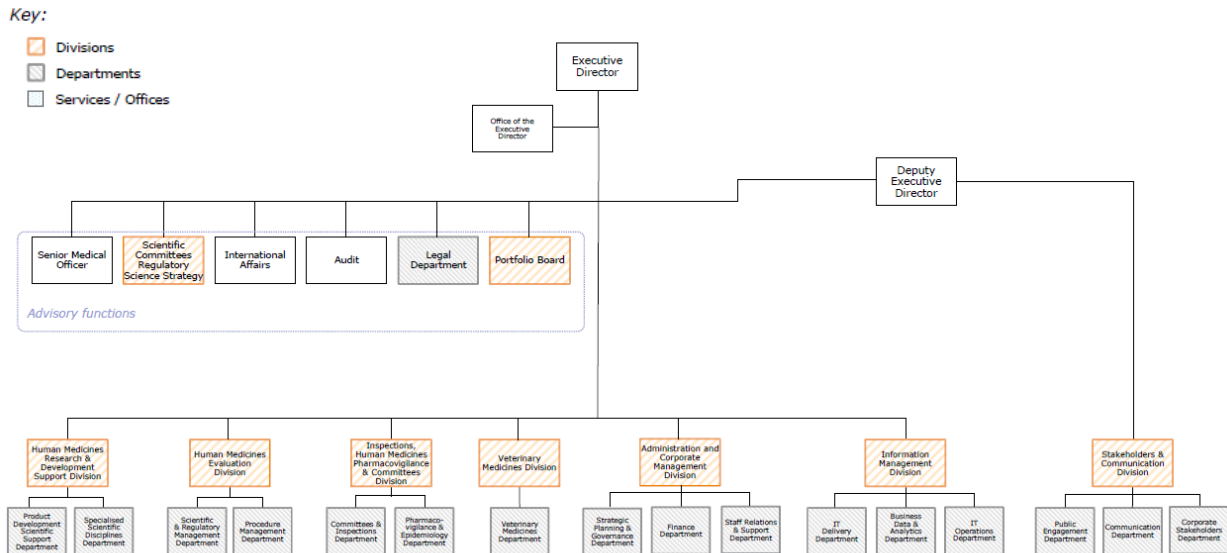
4.2. EMA responsibilities

4.2.1. Executive Director

The EMA Executive Director is the legal representative of the Agency and has overall responsibility for:

- the day-to-day administration and operations, including the EMA pharmacovigilance system (for which he authorises the pharmacovigilance system manual and any change to it);

- the management of all Agency resources;

- the compliance with legal timelines;

- the appropriate coordination between committees and the coordination group;

- all budget and staff-related matters;

- the provision of the secretariat for the EMA Management Board.

The Management Board is the Agency's integral governance body. It has a supervisory role with general responsibility for budgetary and planning matters, the appointment of the EMA Executive Director and the monitoring of the Agency's performance. The Management Board is the EMA supervisory body to which the Executive Director submits for approval each year a draft report covering the activities of the EMA in the previous year and a draft work programme for the coming year.

4.2.2. Heads of division

The heads of division are responsible for the daily operation of the EMA pharmacovigilance tasks within their divisions and for monitoring the quality of the outputs generated under their responsibility.

The heads of divisions through the Medicines Leadership Team are responsible for the overall organisation, effective running and monitoring of their EMA pharmacovigilance tasks.

On the basis of the data and information provided by the other heads of division, the head of Inspections, Human Medicines Pharmacovigilance & Committees Division is responsible for coordinating the monitoring of the EMA pharmacovigilance system.

4.2.3. Governance of EMA management

Figure 3. outlines the EMA governance for human medicines, including pharmacovigilance-related aspects.

Figure 3. EMA governance for human medicines

EMA Management Board (MB)
The supervisory body of the EMA, responsible primarily for budgetary and planning matters. Its mandate includes adoption of the Agency's budget and work programme, and appointment of the Executive Director and the Accounting Officer.

EMA Executive Board (EXB)
The governing body of the Agency that considers both strategic issues, including setting the Agency's long-term strategy, setting short-term priorities and goals, preparing for new legislation, and making policy; and operational issues, including deciding on strategy implementation, planning (including resource planning), project approval and implementation, portfolio of programmes, project pipeline, work programme monitoring, finance, HR, KPIs and risk monitoring, and audit reporting.

Medicines Leadership Team (MLT)
The key governance and decision-making body of the scientific operations that considers escalated product-related issues (pre-PRAC or pre-CHMP), as well as organisational, procedural or regulatory matters. It is supported by the Scientific Committees Regulatory Science Strategy advisory function.

4.2.4. Divisions supporting the functioning of the EMA pharmacovigilance system

4.2.4.1. *Inspections, Human Medicines Pharmacovigilance & Committees Division*

The Division is responsible for human pharmacovigilance, including signal detection and management and monitoring of products on the market. It ensures the coordination of inspections and good practice standards. It deals with incident management in the area of safety and quality of human medicines, in liaison with the European medicines regulatory network. The Division maintains close contact with international partners in the areas of inspection and pharmacovigilance in conjunction with the Agency's International Affairs function.

Furthermore, it provides secretariat for the Agency's scientific committees and takes leadership for the Agency's pharmacovigilance system and epidemiology activities.

4.2.4.2. *Human Medicines Evaluation Division*

This Division manages initial marketing authorisations and post-authorisation procedures (e.g. renewals, annual reassessment, variations, PSURs, PASS), Union procedures and administrative procedures. This means ensuring compliance with scientific, regulatory and procedural requirements and coordinate the internal and external network resources based on the complexity of each procedure.

The Division also manages the overall product lifecycle covering the entire portfolio of products for safety, efficacy, risk management and labelling activities. It provides scientific support to therapeutic areas working parties, drafting groups and scientific advisory groups and provides scientific and regulatory support to committees, by building the necessary scientific expertise and therapeutic area knowledge.

4.2.4.3. *Human Medicines Research & Development Support Division*

The Division is in charge of providing scientific advice on all products and issues related to medicine development, and of proposing measures specifically aimed at fostering development of new medicines in orphan diseases and paediatric populations. The Division also incorporates specialist scientific disciplines that are necessary to ensure a comprehensive assessment, to support and complement the competencies available in the network.

4.2.4.4. *Stakeholders & Communication Division*

The Division is responsible for ensuring that the Agency has a coherent, coordinated and consistent approach to stakeholder and partner relations management and communication.

It manages relations with and information to patients and healthcare professionals, and coordinates medicines information in the European medicines regulatory network. The Division manages the Agency's online presence, external communication and press relations, as well as the information centre. The Division also manages relations with the pharmaceutical industry, and provides support to micro, small and medium-sized enterprises (SMEs) through its SME Office.

4.2.4.5. *Administration and Corporate Management Division*

The Agency's Administration Division is responsible for managing revenue, expenditure and accounts according to existing rules and regulations, for recruiting, managing and administering staff and

seconded personnel, and for providing and running the necessary infrastructure services for the effective functioning of the Agency.

It cooperates closely with the European Parliament and the Council of the European Union (Budgetary Authority), as well as the European Commission, European Court of Auditors and other European agencies on matters relating to administration, the budget, personnel and rules and regulations on finances, audit and accounting.

The Strategic Planning & Governance Department coordinates planning, monitoring, risk management, quality management (including all EMA policies, standard operating procedures and work instructions supporting EMA pharmacovigilance tasks) and internal communication activities.

The Staff Relations & Support Department supports all heads of division in relation to all aspects related to human resources management, such as coordination of recruitment of adequately qualified and experienced EMA staff, and oversight of the development and maintenance of training plans and records supporting EMA pharmacovigilance tasks.

4.2.4.6. Information Management Division

The Division enables the Agency, its staff, members of its committees, working parties and advisory groups, and other stakeholders, to make efficient and effective use of information technology in order to achieve its organisational and policy objectives. It provides high-quality and advanced information-technology-infrastructure solutions and e-services, support services, and unified telecommunications facilities including solutions for physical and virtual meetings, in addition to the information systems required to support Agency corporate business processes.

It is also responsible for product, application and information support to the Agency's operations, management of product databases (e.g. SIAMED, EudraVigilance, PSUR repository) and their data quality and data analysis to support the Agency's decision-making.

It delivers the systems defined in the European Union telematics strategy for use by the European regulatory network, the pharmaceutical industry, healthcare professionals and the general public.

4.2.5. Audit function

The Audit function is responsible for providing to the Executive Director independent, objective assurance and consulting services designed to add value and improve the organisation's operations. The function provides independent and professional audit services, founded on sound values and ethics, to support informed decision-making and accountability across the Agency. The Audit activity helps the Agency to accomplish its objectives by bringing a systematic, disciplined approach to evaluating and improving the effectiveness of risk management, control and governance processes.

The head of the Audit function has overall responsibility for pharmacovigilance audits of EMA pharmacovigilance tasks.

4.2.6. Management Board and Heads of Medicines Agencies Office

The Management Board and Heads of Medicines Agencies Office reports directly to the EMA deputy Executive Director and provides support to the Management Board and Agency management. It also ensures a permanent link between the EMA Executive Director and the EU Member State national competent authorities.

4.2.7. EU Telematics programme

EU Telematics is the collective name for a joint endeavour in the context of the regulation of medicines for human and veterinary use between the European Commission, the EMA and national competent authorities. Together, these make up the EU regulatory network which has shared responsibility for implementing the EU Telematics Strategy.

The EU Telematics Strategy aims to put in place and maintain common information-technology (IT) services to implement European pharmaceutical policy and legislation. These services should be effective, add value and help to optimise support to the EU regulatory network in the regulation of medicines for the protection of human and animal health.

Figure 4. Joint EU Telematics governance model


The joint EU Telematics governance model
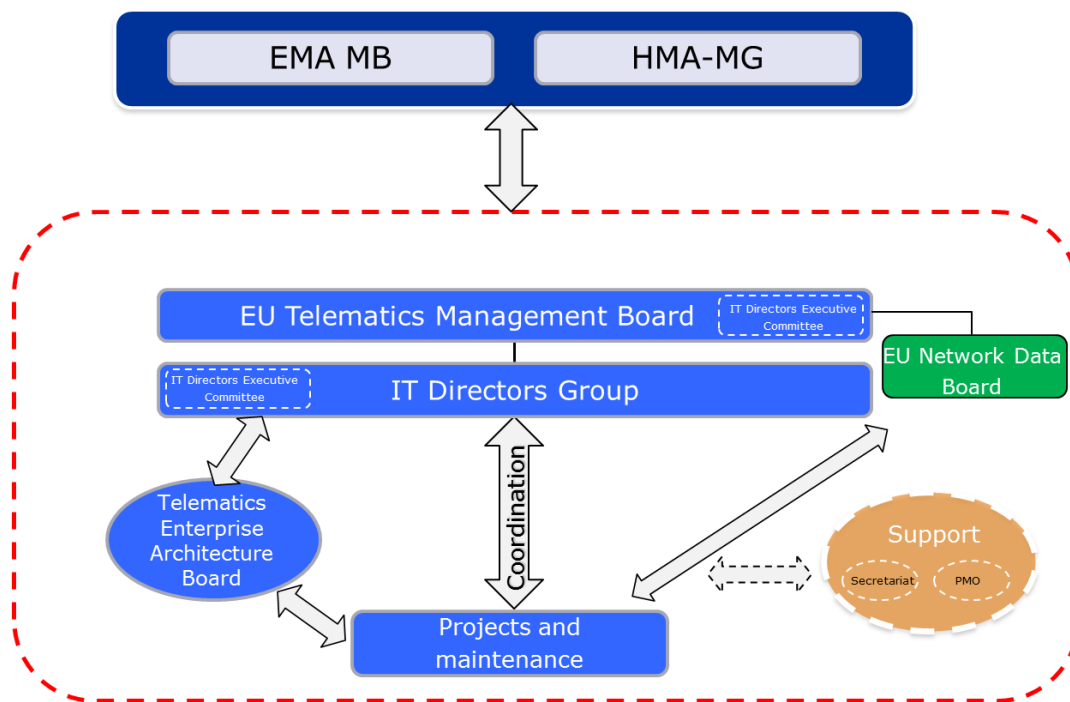
4.3. EMA management responsibility in the quality cycle of the pharmacovigilance system

Figure 5 displays EMA leadership responsibility in the quality cycle related to the pharmacovigilance system. All steps forming part of the quality cycle are described in Article 8 of Commission Implementing Regulation (EU) No 520/2012.

Figure 5. EMA leadership responsibility in the quality cycle (pharmacovigilance system)
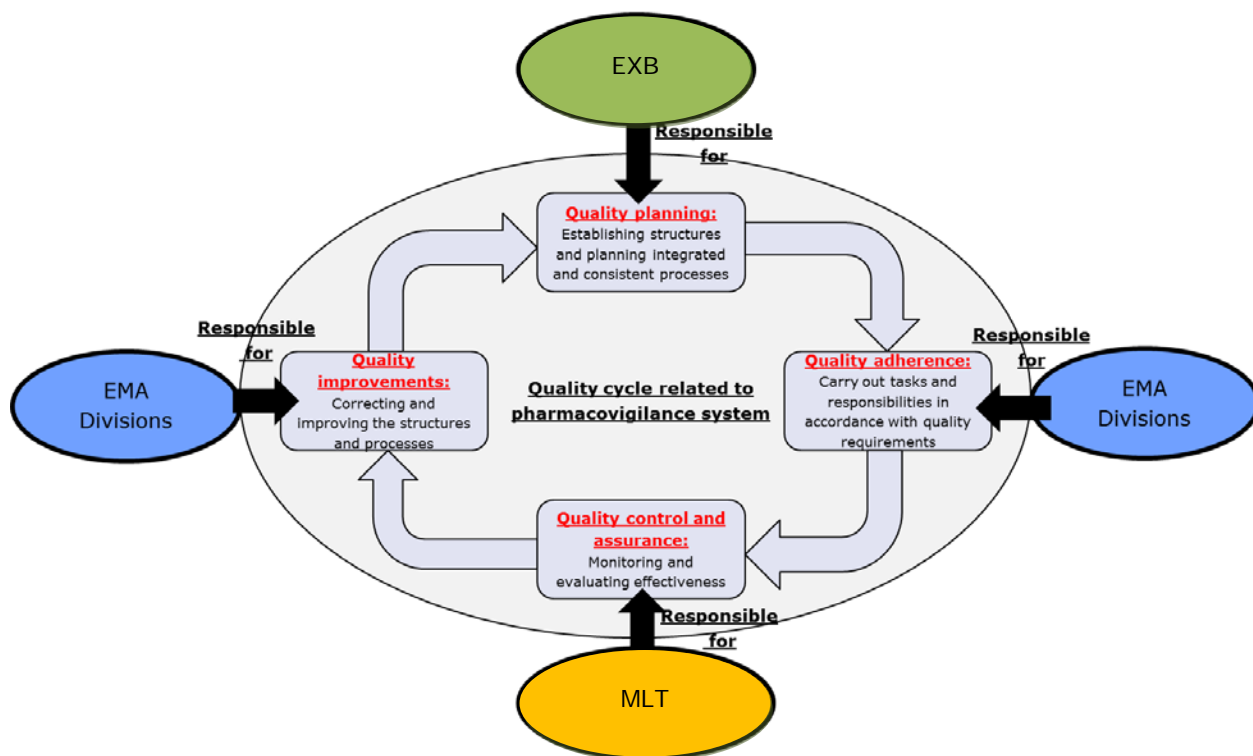
4.4. Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC is the committee at the EMA that is responsible for assessing and monitoring safety issues for human medicines.

The PRAC's recommendations are considered by the CHMP when it adopts opinions for centrally authorised medicines and referral procedures and by the CMDh when it provides a recommendation on the use of a medicine in Member States.

PRAC also advises EMA on the development of guidelines and standards and advices on operational aspects of EU pharmacovigilance.

4.5. Committee for Medicinal Products for Human Use (CHMP)

The 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 post-authorisation emerging safety concerns, procedures for the assessment of PSURs and procedures for post-authorisation safety studies (PASS) for centrally authorised products, as well as 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. For questions related to pharmacovigilance activities and risk-management systems, the CHMP relies on the recommendations of the PRAC.

4.6. Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

The CMDh is responsible for examining any questions relating to marketing authorisations and variations of the terms of the marketing authorisation for medicinal products authorised through the mutual recognition or the decentralised procedure, as well as questions concerning nationally authorised products arising from assessments of periodic safety update reports, non-interventional post-authorisation safety studies and regulatory procedures at EU level. For questions in relation to pharmacovigilance, the CMDh reaches a position, based on a PRAC recommendation, on regulatory procedures at EU level when only nationally authorised products are concerned.

5. EMA pharmacovigilance tasks

The following EMA pharmacovigilance tasks for centrally authorised products and nationally authorised products, where applicable (see also Figure 6), are based both on the EU pharmacovigilance legislation and the good pharmacovigilance practice (GVP) modules:

1. EMA pharmacovigilance system delivering the requirements of the quality system (based on GVP Module I).

2. Pharmacovigilance inspections (based on GVP Module III).

3. Risk-management systems (based on GVP Module V).

4. ADR management (based on GVP Module VI), including ADR collection and management as well as provision of data support and analysis.

5. Periodic safety update reports (based on GVP Module VII), including management of EURD list and the maintenance of the PSUR repository.

6. Post-authorisation studies (based on GVP Module VIII).

7. Signal management (based on GVP Module IX).

8. Emerging safety issues (based on GVP Module IX) and incident management (see Section 12 of this manual).

9. Management of the list of products under additional monitoring (GVP Module X), as well as the list of withdrawn products.

10. Safety communications (based on GVP Module XV).

11. Pharmacovigilance referrals.

12. Guidance coordination (including GVP development) and standards for the system.

13. Training and capacity building, including EU Network Training Centre (EU-NTC) and ENCePP.

14. Monitoring the compliance of marketing-authorisation holders.

15. Coordination of pharmacovigilance enquiries.

16. Coordination of development of best evidence to support regulatory decision-making.

17. Enhancement and maintenance of the EudraVigilance database and data processing network.

18. Establishment and maintenance of Art. 57 database of medicinal products authorised in the EU.

19. Medical literature monitoring.

5.1. Groups of processes covering pharmacovigilance throughout the product lifecycle

In order to build a responsibility assignment matrix (see Figure 6), the EMA pharmacovigilance tasks are set out in five process groups covering pharmacovigilance throughout the product lifecycle:

1. **Collect, manage and analyse**. This process group describes the collection, overall management and analysis, where applicable, of data, information and documents in relation to product safety.

2. **Review and assess**. This process group describes the overall review and analysis (e.g. by rapporteurs) of data, information and documents in relation to product safety.

3. **Decide and act**. This process group describes the overall coordination of decision-making through committees (e.g. PRAC, CHMP) and the coordination group (CMDh).

4. **Communicate**. This process group describes the overall coordination of safety communication.

5. **Monitor**. This process group describes the overall monitoring of implementation and impact of proposed regulatory actions.

6. Responsibility assignment matrix for pharmacovigilance tasks

6.1. Definitions

A responsibility assignment matrix (based on the RACI model, 'responsible, accountable, consulted, informed') describes the cross-functional roles and responsibilities and participation by various EMA divisions in completing pharmacovigilance tasks belonging to the overall EMA pharmacovigilance system.

Although the RACI approach is followed and will be enriched as the organisational structure of the Agency evolves, Figure 6, for simplicity, only displays the EMA divisions accountable for pharmacovigilance tasks embedded within the relevant process domains.

Responsible EMA divisions are those which do the work to achieve the pharmacovigilance task. Accountable EMA divisions (sometimes also referred to as approver or final approving authority) are those divisions ultimately answerable for the correct and thorough completion of the pharmacovigilance tasks. Accountable EMA divisions must sign off on (approve) work that responsible EMA divisions provide.

In the RACI model, 'consulted' refers to those whose opinions are sought by means of a two-way communication, while 'informed' relates to those who are kept up to date on progress, often only on completion of the pharmacovigilance task, by means of a one-way communication.

6.2. EMA responsibility assignment matrix for pharmacovigilance tasks

The responsibility assignment matrix (see Figure 6) was agreed and adopted by the Medicines Leadership Team and endorsed by the EMA Executive Board. It puts emphasis on the groups of processes that support the performance of pharmacovigilance tasks. Information Management Divison is, however, accountable for ensuring appropriate functioning of all IT systems supporting the groups of processes and therefore the pharmacovigilance tasks. Administration and Corporate Management Division plays a key role in human resources management.

In line with the responsibility assignment matrix, specific responsibilities are described in accordance with the requirements of the EMA integrated quality management system.

Figure 6. Responsibility assignment matrix

Accountability for EMA pharmacovigilance tasks		Responsibility per process domain for pharmacovigilance (throughout the product lifecycle)				
Accountable division	EMA pharmacovigilance tasks	1. COLLECT/ MANAGE/ ANALYSE	2. REVIEW/ ASSESS	3. DECIDE/ ACT*	4. COMMU- NICATE	5. MONITOR
P	1. EMA PhV system (GVP M. I)	P	P	P	S	P
P	2. Pharmacovigilance inspections (GVP M. III)	P	P	P	S	P
E	3. Risk-management systems (GVP M. V)	E	E	E	S	E
I	4. ADR management (GVP M. VI)	I	I	I	S	I
E	5. Periodic safety update reports (GVP M. VII)	E	E	E	S	E
E	6. Post-authorisation studies (GVP M. VIII)	E	E	E	S	E
P	7. Signal detection and management (GVP M. IX)	P	P	P	S	P
P	8. Emerging safety issues and incident management	P	P	P	S	P
P	9. Management of list of products under additional monitoring and list of withdrawn products (incl. GVP M. X)	P	P	P	S	P
S	10. Safety communications (GVP M. XV)	S	S	S	S	S
E	11. Pharmacovigilance referrals	E	E	E	S	E
P	12. Guidance coordination and standards	P	P	P	S	P
P	13. Training and capacity building, including EU-NTC and ENCePP	P	P	P	S	P

Accountability for EMA pharmacovigilance tasks		Responsibility per process domain for pharmacovigilance (throughout the product lifecycle)				
Accountable division	EMA pharmacovigilance tasks	1. COLLECT/ MANAGE/ ANALYSE	2. REVIEW/ ASSESS	3. DECIDE/ ACT*	4. COMMU-NICATE	5. MONITOR
E	14. Monitoring of MAHs compliance	E	E	E	S	P
P	15. Coordination of pharmacovigilance enquiries	P	P	P	P	P
P	16. Coordination of development of best evidence to support regulatory decision-making	P	P	P	S	P
I	17. Enhancement and maintenance of the EudraVigilance database and data processing network	I	I	I	S	I
I	18. Establishment and maintenance of Art. 57 database of medicinal products authorised in the EU	I	I	I	S	I
I	19. Medical literature monitoring	I	I	I	S	I

D: Human Medicines Research & Development Support Division
E: Human Medicines Evaluation Division
P: Inspections, Human Medicines Pharmacovigilance & Committees Division
I: Information Management Division
S: Stakeholders & Communication Division
* E-Division is accountable for the functioning of the decision-making through the committees and the CMDh. The divisions highlighted in the table are accountable for appropriately providing the committees with the data, information and documents required to support the overall decision-making process.

7. Human resources management

7.1. Recruitment and training of EMA personnel

In line with relevant EU legislation and the requirements of the EMA integrated quality management system, all EMA staff are recruited on the basis of their adequate qualifications and experience. All incoming and existing EMA personnel receive initial and continued training in relation to their roles and responsibilities.

In liaison with Human Medicines Research & Development Support Division and Human Medicines Evaluation Division, the Inspections, Human Medicines Pharmacovigilance & Committees Division

carries out at least once a year an assessment of training needs related to the performance of EMA pharmacovigilance tasks, taking account of scientific progress and development of new pharmacovigilance concepts. The proposed training needs are presented to the Medicines Leadership Team, which then provides recommendation to the EMA Executive Board.

It is every line manager's responsibility to ensure through the establishment of a job profile that EMA personnel have adequate qualifications, experience and training to undertake their assigned EMA pharmacovigilance tasks (e.g. training needs and plans are reviewed through annual appraisals).

Training is recorded and can be viewed through SAP HR, which is an IT system covering learning solutions for every EMA staff member and line manager, including training (See Annex 1). Training plans are established and monitored regularly to ensure that training needs to ensure adequate performance of the EMA pharmacovigilance tasks are met.

7.2. Job descriptions

Individual roles and responsibilities are documented within job descriptions that are kept up to date in accordance with relevant EMA Policies that relate to the updating of job profiles and job descriptions.

7.3. Declaration of interests

For all EMA personnel and Member State experts, declarations of interests are managed in accordance with the requirements of the EMA integrated quality management system.

8. Computerised systems and databases supporting the EMA pharmacovigilance system

A wide range of computerised systems and databases are used to support efficient functioning of the EMA pharmacovigilance system.

These computerised systems and databases are developed and maintained through both a dedicated EMA and EU IT governance structure (see section 4.2.7. **EU Telematics programme**) and established working methodologies described in accordance with the requirements of the EMA integrated quality management system.

A list of functionality, together with a short description of computerised systems and databases used to support the functioning of the EMA pharmacovigilance system (receipt, collation, recording and exchange of safety information), is displayed in Annex 1.

9. Monitoring the EMA pharmacovigilance system

The EMA is legally required to monitor the performance of its pharmacovigilance system, its structures, processes, outputs and outcomes.

Outputs and outcomes are mainly distinguished by time and measurability. Outputs relate to tangible objects resulting directly from a process or task (e.g. safety communication on the EMA website). Outcomes, on the other hand, relate to the benefits received by stakeholders targeted by the outputs (e.g. changes in prescribing or dispensing behaviours as a result of DHCP letters).

9.1. Definitions of performance and workload measures aligned with quality objectives of the pharmacovigilance system

Performance measures should be aligned with the following overall quality objectives for pharmacovigilance, as set by the EMA Executive Board and laid down in GVP Module I:

- 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;

- contributing to the protection of patients' and public health.

Performance indicators (PIs) can be defined as quantifiable measures that reflect performance in the context of achieving wider goals and objectives of the Agency.

Key performance indicators (KPIs) are indicators most important to a strategic understanding of the Agency's functioning. An appropriate selection of KPIs mitigates the need for several reports on a wide range of measures that may be less relevant.

Workload indicators (WIs) are indicators that measure the amount of work completed, e.g. number of completed procedures, number of adverse drug reaction reports received, etc.

It is the responsibility of Inspections, Human Medicines Pharmacovigilance & Committees Division, which oversees the monitoring of the EMA pharmacovigilance system, to review at least annually the pertinence of all PIs, KPIs and WIs and propose some adjustments for alignment with the wider goals and objectives of the Agency.

It is the overall responsibility of responsible and accountable EMA divisions to monitor the quality of their outputs and to provide Inspections, Human Medicines Pharmacovigilance & Committees Division with the data on the KPIs, PIs and WIs related to their pharmacovigilance tasks, in accordance with the agreed reporting cycle.

9.2. Characteristics of performance and workload measures

Objectives, performance and workload measures (i.e. PIs, KPIs and WIs) are selected and agreed beforehand by the Medicines Leadership Team and adopted by the EMA Executive Board for pharmacovigilance tasks related solely to the EMA and at EMA Management Board level for tasks related to the EU pharmacovigilance system.

Objectives and performance measures must be aligned and take into account SMART elements ('Specific Measurable Achievable Realistic objectives to be achieved within Timelines').

As opposed to performance indicators, key performance indicators relate to key processes where a deviation from target is likely to impact the functioning of the EMA pharmacovigilance system.

The Agency maintains a list of performance indicators and workload indicators. A list of impact indicators is under development in the context of the Impact Strategy and Work Plan adopted by the PRAC in January 2016.

9.3. Reporting cycle

The reporting frequency is defined at Medicines Leadership Team level.

At least on a quarterly basis, the relevant heads of division accountable for a specific set of EMA pharmacovigilance tasks report their PIs, KPIs and WIs to Inspections, Human Medicines Pharmacovigilance & Committees Division.

9.4. *Monitoring tools and mechanisms*

The monitoring of all EMA pharmacovigilance tasks is an ongoing and continuous activity that is built into the EMA pharmacovigilance system.

Heads of division are accountable for setting up effective tools supporting the identification of results of performance measures that could lead to deviations from objectives. In line with agreed frequency, those results of performance measures are reported to Inspections, Human Medicines Pharmacovigilance & Committees Division and reviewed by the Medicines Leadership Team. This management review also takes account, where relevant, of results from internal controls (e.g. ex-post controls) performed according to the requirements of the EMA integrated quality management system.

Any deviation from an objective, together with appropriate action taken, is discussed at Medicines Leadership Team level and escalated to the EMA Executive Board when needed, in accordance with the set escalation criteria.

Further to their agreement at least at Medicines Leadership Team level, the relevant corrective actions and timelines are assigned to the heads of division.

Heads of division are then accountable for undertaking the assigned corrective actions and reporting on their status to Inspections, Human Medicines Pharmacovigilance & Committees Division within the Medicines Leadership Team meeting at least on a quarterly basis.

9.5. *Pharmacovigilance audits*

In accordance with Article 28f of Regulation (EC) No 726/2004, the Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis.

The specificities of the risk-based audits of the Agency's quality system (for pharmacovigilance activities) are as described in Articles 8,14,15,16, 17(1) of Commission Implementing Regulation (EU) No 520/2012 and GVP Module IV – Pharmacovigilance audits. This GVP Module provides guidance on planning and conduct of the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonisation, and encourage consistency and simplification of the audit process through collaboration with the Pharmacovigilance Audit Facilitation Group composed of representatives from the PRAC, Member States and the EMA.

The EMA has an independent internal Audit function, which reports directly to the EMA Executive Director. It is responsible for the planning and conduct of an effective pharmacovigilance audit programme designed to test the EMA pharmacovigilance tasks within the EMA pharmacovigilance system, as well as the provision of reports to the EMA Management Board every two years.

In line with relevant EMA policies, standard operating procedures and work instructions, it is the responsibility of the Head of Audit to plan and ensure appropriate execution of the pharmacovigilance audit programme and to assess its efficacy, as well as ensuring that pharmacovigilance audits and subsequent improvement action plans are adequately documented and implemented, and to report directly to the EMA Executive Director.

It is the responsibility of the head of Inspections, Human Medicines Pharmacovigilance & Committees Division to report on at least a quarterly basis to the Medicines Leadership Team on the progress related to the implementation of corrective actions, particularly if there are corrective actions linked to critical findings.

10. Business continuity arrangements

The EMA pharmacovigilance system is operated in accordance with the requirements of the EMA integrated quality management system, as well as plans related to business continuity arrangements.

11. Incident management plans

An incident management plan for human medicines has been in operation within the EU regulatory network since September 2009.

The EU regulatory network incident management plan for medicines for human use aims to ensure that the most appropriate actions are taken across the EU whenever incidents (new events or information) arise concerning human medicines. It covers medicines authorised centrally, nationally and through the decentralised and mutual-recognition procedures.

The plan's execution involves representatives from the Agency, the European Commission and medicines regulatory authorities in the EU Member States.

Annex 1 - Non-exhaustive list of computerised systems supporting the functioning of the EMA pharmacovigilance system

EudraVigilance

EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

EudraVigilance supports the following:

- the electronic exchange of suspected adverse reaction reports (known as individual case safety reports) between the European Medicines Agency, national competent authorities, marketing-authorisation holders, and sponsors of clinical trials in the EEA;

- the early detection of possible safety signals associated with medicinal products for human use;

- the continual monitoring and evaluation of potential safety issues in relation to reported adverse reactions;

- the decision-making process, especially in the form of risk management, based on a broader knowledge of the adverse reaction profile of medicinal products, based on information collected through the EudraVigilance Medicinal Products Dictionary (XEVMPD), also known as Article 57 database.

SAS

SAS is a set of informatics tools used by Information Management Division to support any activities related to data management, data analytics and business intelligence.

EPITT

EPITT (European Pharmacoviglance Issues tracking Tool) is a database developed by the EMA to promote the rapid communication of pharmacovigilance and risk-management issues between the EMA, all national competent authorities (NCAs) of the European Economic Area (EEA), the CHMP, the PhVWP/PRAC and the CMDh. EPITT provides access to documents related to the safety of medicinal products/substances authorised in the EEA. It is also an easy query tool accessible to the scientific colleagues of all the NCAs and all EMA staff members.

SIAMED II

SIAMED II is the Agency's product information and application tracking system. It is used for managing:

- pre-submission activities;

- applications within the centralised procedure;

- fee calculation;

- managing product data;

- maximum residue limits;

- post-authorisation measures and PSURs.

The information it stores is also used to generate most of the Agency's procedural documents, such as scientific opinions or template letters, as well as a growing number of statistics. It also supports other business applications such as SAP and EudraPharm.

DREAM

The DREAM (Document Records Electronic Archive Management) system combines two older systems:

- EDMS (Electronic Document Management system), since 2004;

- MMD (Managing Meeting Documents), since 2006/2007.

DREAM is a single, web-based system with added functionality, including search, the ability to set retention periods and a simplified tabling feature in MMD. The DREAM system has been available since 9 August 2010.

EudraCT

EudraCT is the EU's electronic database of clinical trials. It contains information submitted by sponsors and informs users about ongoing clinical trials in all EEA countries, enabling an overview of multi-state trials.

- From here, users can create a clinical-trial application (CTA) for a trial to be conducted within the EEA. Once completed, it is ready for submission to a national competent authority or an independent ethics committee.

- Registered users can log in to the system to perform tasks relating to their roles.

- XML documents of the CTA or third-country clinical-trial information can be uploaded using the Load button.

- Allows users to create, update, validate and post result data sets, and load summary attachments to the EudraCT database.

EudraGMP

EudraGMDP is the name for the EU database referred to in Article 111(6) of Directive 2001/83/EC and Article 80(6) of Directive 2001/82/EC. It contains the following information:

- manufacturing and import authorisations;

- good manufacturing practice (GMP) certificates;

- statements of non-compliance with GMP;

- GMP inspection planning in third countries.

In addition, the following new information is required in the database since 2013 (as data transfers from national systems can be complex, it will take several months for all the national competent authorities to complete the uploading of this data):

- wholesale distribution authorisations;

- Good Distribution Practice (GDP) certificates;

- statements of non-compliance with GDP;

- registration of manufacturers, importers and distributors of active substances for human use located in the EEA.

Almost all information uploaded into the database is available to the public. National competent authorities are able to exclude some information from public view. This includes information of a commercially sensitive or personal nature, inspection planning and information that may need to be restricted in the interests of security.

IMS dataset

The EMA has procured access to over 30 million electronic medical records of patients in Germany, the UK and France by means of a licence through IMS Health Ltd. The data are used for in-house pharmacoepidemiology studies.

THIN dataset

THIN is a medical research database of anonymised UK patient records from information entered by general practices. The EMA has access to it by means of a procured licence. It is used for in-house pharmacoepidemiology studies.

ENCePP databases

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established in 2006 by the Agency in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The network is comprised of research centres, existing networks and data sources. Its goal is to further strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on benefit-risk, using available expertise and research experience across Europe.

Studies database

The E-Register of Studies (EU Post-Authorisation Studies (PAS) register) aims to provide a publicly accessible resource for the registration of pharmacoepidemiological and pharmacovigilance studies. Its purpose is to:

- increase transparency;

- reduce publication bias;

- facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing-authorisation holders and the public;

- promote information exchange;

- facilitate collaboration within the scientific community;

- facilitate optimal use of pharmacoepidemiology and pharmacovigilance expertise in Europe by preventing unnecessary duplication of research;

- act as the publicly available EU electronic register of post-authorisation studies (EU PAS Register) referred to in GVP Module VIII on post-authorisation safety studies (PASS);

- For non-interventional PASS conducted voluntarily or pursuant to an obligation, GVP Module VIII requires the marketing-authorisation holder to make study information (including for studies conducted outside the EU) available in the EU PAS Register.

Pharmacoepidemiological or pharmacovigilance studies applying for the ENCePP Seal must be registered in the ENCePP E-Register of Studies before the study commences, but also any other non-interventional study not formally applying for the ENCePP Seal should be registered voluntarily, to ensure transparency.

ENCePP resources database

The ENCePP Database of Research Resources is an electronic index of available EU research organisations and data sources in the field of pharmacoepidemiology and pharmacovigilance. It is publicly available through the ENCePP web portal.

The database serves as a central resource for both researchers and study sponsors seeking to identify organisations and data sets for conducting specific pharmacoepidemiology and pharmacovigilance studies in Europe.

It comprises two indices: the *Inventory of ENCePP research centres* and the *Registry of EU data sources*. Both the Inventory and the Registry are fully searchable and allow the identification of centres and data sets by country, type and many more relevant keywords.

SAP HR

SAP HR is an IT system that includes for every EMA staff member and line manager learning solutions (training and IQM manual), travel and expense management (missions and training missions) and appraisals management (workflow for contract renewals). SAP HR also allows recording of each staff member's working hours, requesting absence electronically and managing posts in line with the establishment plan.

JIRA application

JIRA is the request management software used for managing requests for information and formal requests for access to documents, which builds upon the web form already available on the Agency's website. It is essential for addressing stakeholder queries.

TrackWise

TrackWise is the EMA's electronic audit management system. This software is used for tracking the Agency's processes and the creation and archiving of related records and associated document.

PSUR repository

The PSUR repository is a single, central platform for PSURs and related documents to be used by all regulatory authorities and pharmaceutical companies in the EU. The PSUR Repository provides an important simplification for marketing authorisation holders allowing them to send all PSURs and related submissions to a single recipient. It also facilitates the assessment by ensuring that NCAs, EMA and its scientific committees have timely and secure access to all relevant documents. The PSUR Repository was introduced by the EU pharmacovigilance legislation to facilitate the exchange of information on the safety of authorised medicines between regulators and pharmaceutical companies and it supports all PSURs irrespective whether they are for centrally or nationally authorised medicinal products and whether they follow the EU single assessment or purely national PSUR procedure. The use of the PSUR Repository is mandatory for all PSUR submissions as of 13 June 2016.