

Pharmacovigilance Systems and Quality systems

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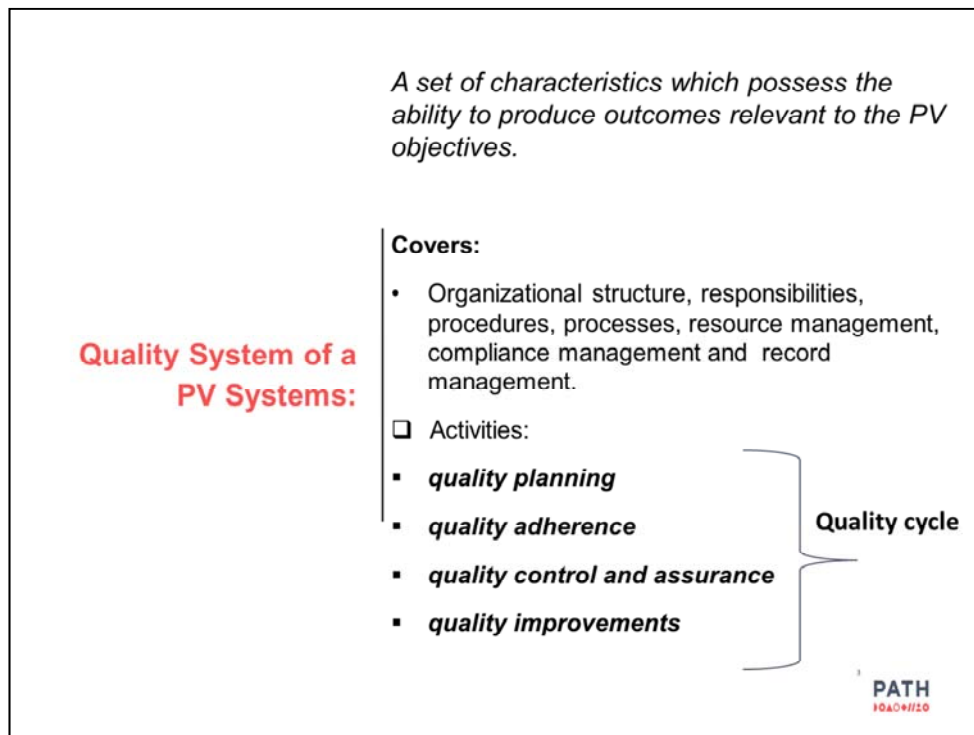
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Pharmacovigilance System

System used by an organization to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance .

Is characterized by its structures, processes and outcomes



All the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It shall cover organizational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.

☐ Thus, the activities on which the quality system should be based on are:

- **quality planning**
- **quality adherence**
- **quality control and assurance** and
- **quality improvements**

Since, these activities are required to be continuously undertaken they are referred as “**quality cycle**”.

PV and Quality...

- ❑ **Quality objectives** includes:
 - **Compliance** with the legal requirements
 - **Prevention** of harm from adverse reactions
 - **Promotion** of safe and effective use of medicinal products,
 - **Contribution** in the protection of patients' and public health

- ❑ For PV system, the **quality objectives** includes:
 - **Compliance** with the legal requirements for PV tasks and responsibilities;
 - **Prevention** of 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;
 - **Promotion** of safe and effective use of medicinal products, in particular by providing timely information about the safety of medicinal products to patients, healthcare professionals (HCPs) and the general public; and
 - **Contribution** in the protection of patients' and public health

Company's Responsibilities Pertaining to Quality Systems

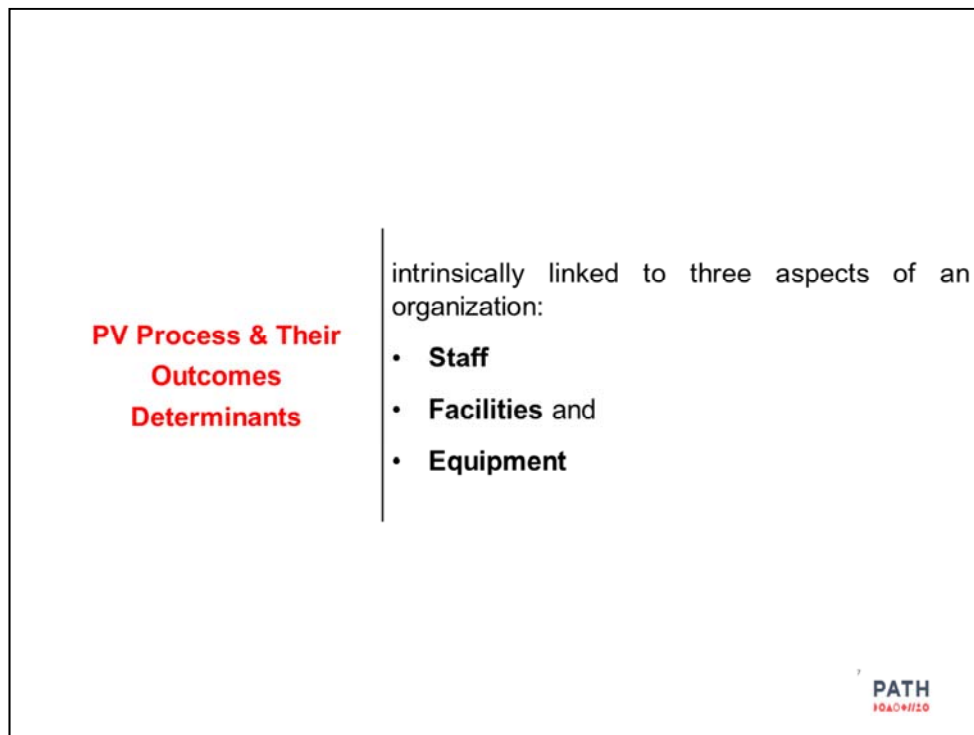
☐ **Staff** should be:

- **adequate**,
- **competent**, and
- appropriately **qualified and trained**

Company's Responsibilities Pertaining to Quality Systems

❑ Organizational managerial staff should ensure that:

- Quality system is **documented**
- Documents are subjected to **control** (creation, revision, approval and implementation)
- **Resources** including human, facilities, equipment, etc. are sufficient and appropriate
- **Compliance** and **record management** is adequate
- Timely and effective **communication mechanism** including concern escalation process
- PV system and its quality system are
 - **reviewed** periodically
 - the **concern(s)** regarding suspected non-adherence to the requirements are identified & investigated and
 - **corrective and preventive measures and/or escalation** action, where necessary, are introduced
- **Audits** are conducted



The quality conduct of PV process and their outcomes is intrinsically linked to three aspects of an organization i.e. **staff, facilities and equipment's**

- ❑ The staff being the critical aspect, their training on the PV requirements becomes essential and so the organization's responsibility is to:
 - provide initial and continued training
 - maintain training plans and records
 - training should be plan based on the needs assessment and subject such plans to monitoring
 - training provide should be such that it:
 - supports continuous improvement of relevant skills, the application of scientific progress and professional development
 - ensures that staff has appropriate qualifications, understanding of relevant PV requirements as well as experience for the assigned tasks and responsibilities

➤ ensure that staff

receives and is able to seek information on the course of action once s/he becomes aware of a safety concern

receives appropriate instructions on the processes to be used in case of urgency

not having any specific related role but whose activities may impact the PV system or its conduct are adequately trained

❑ Considering the importance of facilities and equipment, the organization should:

➤ have adequate facilities and equipment such as office space, information technology (IT) systems and (electronic) storage space

➤ they should be located, designed, constructed, adapted and maintained so as to suit their intended purpose

➤ ensure that the critical ones are subjected to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose

➤ have processes in place to keep awareness of the valid terminologies in their valid versions and

➤ keep the IT systems up-to-date accordingly

Presentation flow...

- ✓ Role of QPPV
- ✓ Role of Staff and Management
- ✓ Facilities and equipment for Pharmacovigilance
- ✓ Training of personnel for Pharmacovigilance
- ✓ Compliance Monitoring
- ✓ Documentation and Record management
- ✓ Critical PV Process and Business Continuity

Qualified Person for Pharmacovigilance (QPPV)

QPPV is **responsible by law** for the safety of a human pharmaceutical product within the EEA.

The QPPV should have a **formal written contract** and an **SOP** clearly defining the QP's roles, functions and responsibilities.

These responsibilities include the **oversight, structure, performance and maintenance** of the PV system in the MAH.

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A Qualified Person for Pharmacovigilance is an individual residing within the European Economic Area (EEA), who is personally responsible by law for the safety of a human pharmaceutical product within the EEA. Applicants for Marketing Authorization have to provide regulatory authorities with a proof that the services of a QPPV are permanently and continuously in place.

The QPPV should have a formal written contract and there should be an SOP clearly defining the QP's roles, functions and responsibilities. These responsibilities include the oversight, structure, performance and maintenance of the PV system in the MAH.

QPPV: Key Roles

Establishing and maintaining a PV system

- Single point of contact for Competent Authorities (CA) on a 24-hour basis
- Contact point for audits/inspections.
- Overseeing the safety profiles of marketed products
- Submission of all PV-related documents
- Quality management system (QMS) including audits, inspections, Corrective Action, Preventive Action plans (CAPAs)

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Establishing and maintaining a pharmacovigilance system; Acting as:

single point of contact for Competent Authorities on a 24-hour basis;

contact point for audits/inspections.

Overseeing the safety profiles of marketed products and any emerging safety concerns;

Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and Good Vigilance Practices;

A quality management system (QMS) is in place which includes audits, inspections, Corrective Action, Preventive Action plans (CAPAs) as needed and that they are actually put in place and completed.

QPPV: Key Roles (contd.)

- Relevant information (benefit-risk evaluation) to the CAs
- Up-to-date Pharmacovigilance System Master File (PSMF)
- Update SOPs and Working Documents
- Metrics & Key Performance Indicators on expedited and aggregate reporting
- PV training: PV departments/ vendors/third parties, etc.
- Written agreements with other companies

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Pharmacovigilance
Assessment
Toolbox

Ensuring a full and prompt response to any request from national Competent Authorities and from the European Medicines Agency;

Providing any other information relevant to the benefit-risk evaluation to the Competent Authorities in Members States and the EMA;

Ensuring and verifying that the Pharmacovigilance System Master File (PSMF) is constantly up-to-date and reflects the current pharmacovigilance system.

SOPs and Working Documents covering PV are in place, up-to-date, trained on and actually followed.

Metrics & KPIs on expedited and aggregate reporting and other key operational functions are tracked.

Ensuring that PV training is done in the drug safety/PV department as well as anywhere (everywhere) else in the company (or vendors, third parties etc.) where safety matters may arise

Ensuring that written agreements with other companies (including business partners, vendors, other third parties) are in place regarding safety and oversee their work.

Ensuring that the appropriate persons are in place and trained to capture AEs.

Ensuring that ICSRs, PSURs and Post-Authorization Safety Studies (PASS)

cases and any other safety commitments are reported appropriately to the competent authorities (CAs).

QPPV: Requirements

The person who is the QPPV must be:

- Appropriately qualified in the theoretical and practical knowledge of PV
- Experienced in all areas of PV
- *Registered with the EMA (as is the deputy)*
- Available 24/7
- Be a single point of contact for PV issues
- Available for PV inspections
- Have access to a physician if the QPPV is not a physician
- The QPPV may delegate tasks.

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Appropriately qualified in the theoretical and practical knowledge of PV. This is not further defined and thus leaves a lot of leeway.

Experienced in all areas of PV

Must work and reside in the EU/EEA (i.e. Norway, Iceland, Lichtenstein)

Registered with the EMA (as is the deputy)

Available 24/7 – either the QPPV or deputy

Be a single point of contact for PV issues

Available for PV inspections

Have access to a physician if the QPPV is not a physician

The QPPV may delegate tasks. If so, this should be done in writing and an oversight system for the out-sourced function be put in place. The QPPV (and MAH) still maintains responsibility for delegated tasks.

Role of Staff and Management

The staff being the critical aspect, their training on the PV requirements becomes essential.

❑ Organization's responsibility:

- Provide initial and continued training
- Maintain training plans and records
- ensures that staff has appropriate qualifications, understanding of relevant PV requirements as well as experience
- Ensure that staff
 - receives and is able to seek information on the course of action once s/he becomes aware of a safety concern
 - understands processes to be used in case of urgency

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- ❑ The quality conduct of PV process and their outcomes is intrinsically linked to three aspects of an organization i.e. **staff, facilities and equipment's**
- ❑ The staff being the critical aspect, their training on the PV requirements becomes essential and so the organization's responsibility is to:
 - provide initial and continued training
 - maintain training plans and records
 - training should be plan based on the needs assessment and subject such plans to monitoring
 - training provide should be such that it:
 - supports continuous improvement of relevant skills, the application of scientific progress and professional development
 - ensures that staff has appropriate qualifications, understanding of relevant PV requirements as well as experience for the assigned tasks and responsibilities
 - ensure that staff
 - receives and is able to seek information on the course of action once s/he becomes aware of a safety concern

receives appropriate instructions on the processes to be used in case of urgency

not having any specific related role but whose activities may impact the PV system or its conduct are adequately trained

Role of Staff and Management (contd.)

- The organization should:
 - have **adequate facilities** and equipment such as office space, information technology (IT) systems and (electronic) storage space
 - they should be located, designed, constructed, adapted and maintained so as to suit their **intended purpose**
 - ensure that the critical ones are subjected to appropriate **checks**, qualification and/or validation activities to prove their suitability for the intended purpose
 - have processes in place to keep awareness of the valid terminologies in their **valid versions** and
 - keep the **IT systems** up-to-date accordingly

Training of personnel for Pharmacovigilance

- Initial and continued training
- Documenting training plans and records
- Continuous improvement of relevant skills, application of scientific progress and professional development
- Process in place to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance, or to identify unmet training needs
- Training for non-PV team staff

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✓All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training .For marketing authorization holders, this training shall relate to the roles and responsibilities of the personnel.

✓The organization shall keep training plans and records for documenting, maintaining and developing the competences of personnel .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 organization should receive and be able to seek information about what to do if they become aware of a safety concern.

✓Process in place 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,

✓Adequate training should also be considered by the organization 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 clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Compliance Monitoring

- **continuous monitoring** of PV data
- **examination** of risk minimisation and prevention
- **scientific evaluation** of all information on the risks of medicinal products, in particular adverse reactions (ADR) within or outside its marketing authorisation terms
- **submission** of accurate and verifiable data on both serious and non-serious ADRs to the authorities within the legally required time-limits
- **quality, integrity** and **completeness** of the information submitted on the risks, including processes to avoid duplicate submissions and to validate signals

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❑ MAH should have the specific quality system procedures and processes which ensures:

- **continuous monitoring** of PV data
- **examination** of risk minimisation and prevention options and that appropriate measures are taken
- **scientific evaluation** of all information on the risks of medicinal products, in particular adverse reactions (ADR) within or outside its marketing authorisation terms
- **submission** of accurate and verifiable data on both serious and non-serious ADRs to the authorities within the legally required time-limits
- **quality, integrity** and **completeness** of the information submitted on the risks, including processes to avoid duplicate submissions and to

validate signals

Compliance Monitoring (contd.)

- **update** of product information
- **effective communication** with CA, including communication on:
 - new or changed risks,
 - PSMF
 - risk management systems including risk minimisations measures, CAPA,
 - PSURs (Periodic Safety Update Reports)
- **appropriate system** for communication of relevant safety information to healthcare professionals and patients

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❑ MAH should have the specific quality system procedures and processes which ensures:

- **continuous monitoring** of PV data
- **examination** of risk minimisation and prevention options and that appropriate measures are taken
- **scientific evaluation** of all information on the risks of medicinal products, in particular adverse reactions (ADR) within or outside its marketing authorisation terms
- **submission** of accurate and verifiable data on both serious and non-serious ADRs to the authorities within the legally required time-limits
- **quality, integrity** and **completeness** of the information submitted on the risks, including processes to avoid duplicate submissions and to

validate signals

Documentation and Record Management

The organization 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.

- ❑ At each stage of PV data storage and processing, ensure
 - specific measures are taken in terms of data security and confidentiality
 - restricted access to documents and databases to authorised personnel only

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➤ The organization 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.

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.

Documentation and Record Management (contd.)

❑ The quality system should be documented by:

- documents on organisational structures and assignments of tasks to personnel
- training plans and records
- instructions for the processes to be used in case of urgency, for compliance management, etc.
- performance indicators
- audits and follow-up audits reports

Additional documentation:

- **organisational chart**
- **organization structure** with job descriptions

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❑ The quality system should be documented by:

- documents on organisational structures and assignments of tasks to personnel;
- training plans and records;
- instructions for the processes to be used in case of urgency, for compliance management, etc.;
- performance indicators where they are used to continuously monitor the good performance of PV activities;
- reports of quality audits and follow-up audits, including their dates and results

❑ The other recommended means for the documentation includes:

- the methods of monitoring the operation of the

quality system and its ability to fulfil the quality objectives;

- a record management policy;
- records created as a result of PV processes;
- records and reports relating to the facilities and equipment

records demonstrating that:

- deficiencies and deviations from the established quality system are monitored,
- corrective and preventive actions have been taken,
- solutions have been applied to deviations or deficiencies and
- the effectiveness of the actions taken has been verified

The additionally documentation required by MAH and NCA includes:

❑ For MAH:

- an **organisational chart** defining the hierarchical relationships of managerial, supervisory and other staff
- the **organization structure** with job descriptions defining the tasks, responsibilities and authorities;

Critical PV Processes and Business Continuity

- Safety profile **monitoring and benefit-risk evaluation** of authorised medicinal products;
- **Risk management** systems
- Individual Case Safety Reports (**ICSRs**)
- **Signal** management
- Periodic safety update reports (**PSURs**)
- Meeting and **responses to competent authorities'** requests
- **Interaction** between the PV and product quality defect systems
- **Information/safety concerns communication**, in particular about the changes to the risk-benefit balance
- **Updated** product information
- **Implementation of variations** to authorisations for safety reasons

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- ☐ Safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- ☐ Establishment, assessment and implementation for risk management systems and evaluation of the effectiveness of risk minimisation
- ☐ Individual case safety reports (ICSRs) - collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission;
- ☐ Signal management;
- ☐ Periodic safety update reports - scheduling, preparation submission and assessment;
- ☐ Meeting commitments and responses to competent authorities' requests;
- ☐ Interaction between the PV and product quality defect systems;

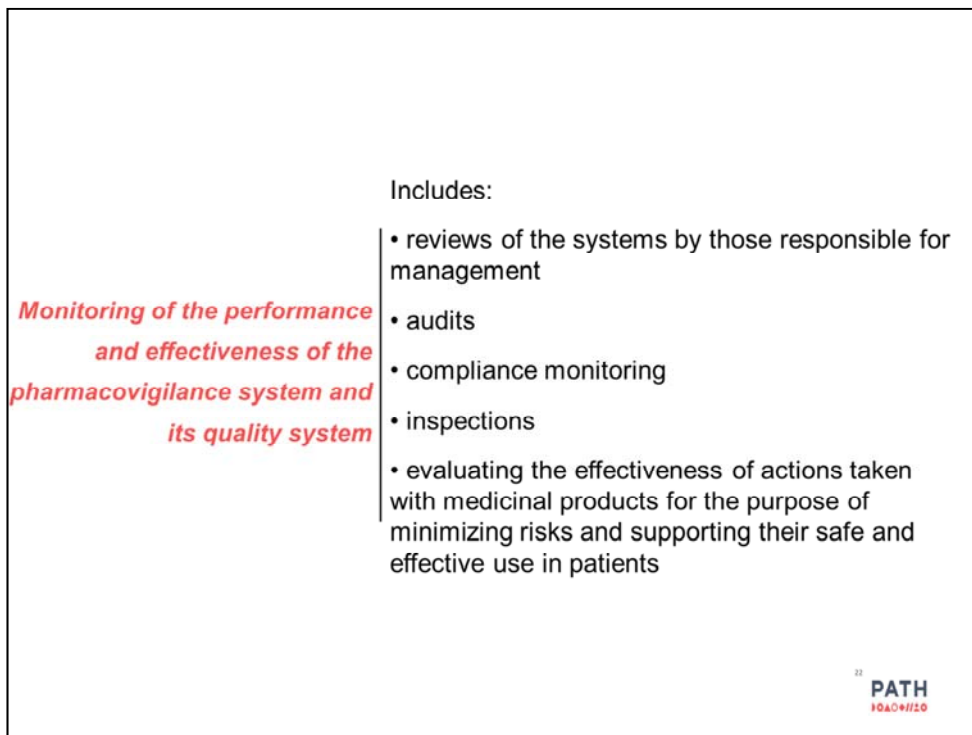
- ❑ Information/safety concerns communication , in particular about the changes to the risk-benefit balance;
 - between MAH and NCA
 - to patients and healthcare professionals

Critical PV Processes and Business Continuity (contd.)

- From business continuity point of view, include:
 - provisions for events that severely impact
 - the organisation's staff and infrastructure in general or
 - on the structures and processes for PV in particular
 - back-up systems for urgent exchange of information
 - within an organisation,
 - amongst organisations sharing PV tasks as well as
 - between MAH and NCA

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- From business continuity point of view, include:
 - provisions for events that severely impact
 - the organisation's staff and infrastructure in general or
 - on the structures and processes for PV in particular
 - back-up systems for urgent exchange of information
 - within an organisation,
 - amongst organisations sharing PV tasks as well as
 - between MAH and NCA



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 minimizing risks and supporting their safe and effective use in patients.

References

1) Guideline on good pharmacovigilance practices (GVP) – Module I EMA/541760/2011

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf