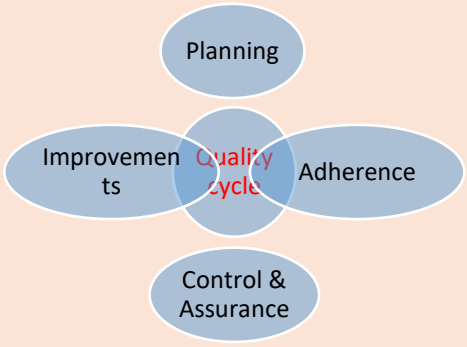
Pharmacovigilance is an activity contributing to the protection of patients 'and public health **by;**

preventing harm from adverse reactions in humans	promoting the safe and effective use of medicinal products

GVP: Modules

Module I – Pharmacovigilance systems and their quality systems

A pharmacovigilance system is designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance using quality systems that are adequate and effective for the PV performance. It is used by an organization, marketing authorization holder and by medicine authorities to fulfill its legal tasks and responsibilities in relation to pharmacovigilance.
Quality requirements are those characteristics of a system that are likely to produce the desired outcome or quality objectives.



- Principles for good pharmacovigilance practices should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities.
- For the purpose of a systematic approach towards quality in accordance with the quality cycle; managerial staff (i.e. staff with management responsibilities) should be available in any organization responsible for the quality system performance.

Responsible for:

1. Ensuring that the organization documents the quality system are subject to document control.
2. Ensuring that suitable and sufficient premises, facilities and equipment are available.
3. Ensuring adequate Resources, compliance management, training & record management are available
4. reviewing the pharmacovigilance system including its quality system at regular intervals
5. 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
6. ensuring that audits are performed
7. motivating all staff members
8. Assigning roles, responsibilities and authorities to staff members.

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organization is intrinsically linked with:

- the availability of a sufficient number of competent and appropriately qualified and trained personnel
- Appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space.

Specific quality system procedures and processes:

1. Compliance management by marketing authorization holders
2. Compliance management by national medicines authorities

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. This shall be put in place for all documents used for pharmacovigilance activities.

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 plan (objectives/processes)
- Quality manual (scope of quality system/processes achieved)
- Quality record (results)

The documentation of the quality system also includes:

1. the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfill the quality objective
2. records created as a result of pharmacovigilance processes
3. records and reports relating to the facilities and equipment
4. 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.

Critical pharmacovigilance processes and business continuity:

1. continuous safety profile monitoring and benefit-risk evaluation of authorized medicinal products
2. risk management systems and evaluating the effectiveness of risk minimization;
3. collection, processing, management, quality control, follow-up for missing information
4. submission and assessment of periodic safety update reports
5. meeting commitments and responding to requests from national medicines authorities
6. communication about safety concerns between marketing authorization holders and national medicines authorities
7. communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products
8. keeping product information up-to-date with the current scientific knowledge

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

1. Reviews of the systems by those responsible for management;
2. audits;
3. compliance monitoring;
4. inspections;
5. Evaluating the effectiveness of actions taken with medicinal products for the purpose of minimizing Risks and supporting their safe and effective use in patients.

Operation of Pharmacovigilance systems in Arab Countries:

The marketing authorization holder in the Arab Country concerned is responsible for the respective pharmacovigilance tasks and responsibilities in order to assure responsibility and liability for its authorized medicinal products **by** operating a pharmacovigilance system and shall establish and use a quality system.

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorization in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorization holder for all authorized medicinal products.

The applicant or the marketing authorization holder is also responsible for developing and maintaining product-specific risk management systems.

- As part of the pharmacovigilance system, the marketing authorization holder shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance **(QPPV)** in the Arab Country concerned. For multinational MAHs a Local Safety Responsible **(LSR)**
- The marketing authorization holder shall submit the name and contact details of the QPPV/LSR to the national medicines authorities
- Each Pharmacovigilance system can have only one QPPV

The marketing authorization holder shall ensure that the QPPV:

I. Has authority to influence the performance of the quality system and the pharmacovigilance activities
II. has access to the pharmacovigilance system master file (PSMF) as well as authority over it
III. can fulfill the responsibilities by ensuring that mechanisms, structures & processes are in place so that the QPPV receives all relevant information as:
    1. emerging safety concerns and benefit-risk evaluation
    2. ongoing or completed clinical trials
    3. information from sources other than from the specific marketing authorization holder as from contractual arrangement
    4. the procedures relevant to pharmacovigilance
VI. Able to obtain information from the database, for example, to respond to urgent requests for information from the national medicines authorities, at any time.

QPPV should be aware of:

1. Regular reviews of the quality system
2. Compliance information
3. scheduled pharmacovigilance audits

4. Notified if a marketing authorization holder intends to expand its product portfolio so that 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.
5. When a marketing authorization holder intends to establish a partnership with another marketing authorization holder, organization or person that has a direct or indirect impact on the pharmacovigilance system to be involved in the preparation of the corresponding contractual arrangements.

Qualifications of the qualified person responsible for pharmacovigilance in the Arab Country concerned:

1. Minimum of bachelor degree of pharmacy or medicine,
2. Basic training in epidemiology and biostatics & training in relation to its pharmacovigilance system,
3. Have the skill for the management of pharmacovigilance systems
4. Knowledge of national pharmacovigilance requirements and experience in pharmacovigilance.

Role of the QPPV:

1. Ensure that the back-up person has all necessary information to fulfill the role
2. Establishment and maintenance of the marketing authorization holder‘s pharmacovigilance system and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements
3. Have access to the pharmacovigilance system master file (PSMF) (ensure accurate and up-to-date reflection of the pharmacovigilance system)

+ Additional **roles related to medicinal products covered by PV system.**

Overall pharmacovigilance responsibilities within each of the Arab Countries:

The national medicines authorities in the Arab Countries are responsible for the respective pharmacovigilance tasks and responsibilities in order to ensure that appropriate action can be taken, when necessary.

- **Role of the national medicines authorities** Each national medicines authority in an Arab Country must operate a pharmacovigilance system [through its National Pharmacovigilance and Drug Safety Centre/ Directorate (NCP)]
  1. Responsible for the safety monitoring of each medicinal product
  2. Monitor the compliance of the marketing authorization holder with national legal Pharmacovigilance Requirements.
- The **role of the Pharmacovigilance advisory committee** is to provide advice on the safety of medicinal products for human use and the investigation of adverse reactions, in order to enable effective risk identification, assessment and management, in the pre- and post-authorization phase leading to recommendations on action at the request of the national medicines authority for products available in relevant Arab Country.

Module II - Pharmacovigilance system master file

- It is a detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products.
- It shall be **located** either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates, irrespective of the format (paper-based or electronic format file).
- Each national medicines authority in the Arab Countries should manage a national list/database which provides a practical mechanism for maintaining up-to-date information about the MAH's (or contractual partner) pharmacovigilance system master file, its status, its location, the QPPV&/or LSR contact information and the products relevant to the pharmacovigilance system described in the pharmacovigilance system master file.
- Any changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system.
- Where applicable, a list of all pharmacovigilance system master files held by the same marketing authorization holder shall be provided in the annex; this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).
- The pharmacovigilance system master file shall be continuously accessible to the QPPV and to the national medicines authorities on request
- permanently available for inspection
- should be submitted in a readable electronic format or clearly arranged printed copy

The Hardcopy Cover Page should include:

1. The unique number assigned by the national medicines authority to the pharmacovigilance system master file (if applicable).
2. The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
3. The name of other concerned MAH(s) (sharing the pharmacovigilance system)
4. The list of pharmacovigilance system master files for the MAH (concerning products with a different pharmacovigilance system)
5. The date of preparation / last update

Information to be contained in the PSMF:

The pharmacovigilance system master file shall contain at least all of the documents described in the following subsections. The pharmacovigilance system master file shall include documents to describe the pharmacovigilance system. The content of the pharmacovigilance system master file should reflect the global availability of safety information for medicinal products authorized in the Arab Country concerned.

I. **QPPV:** description of the responsibilities, CV + its role, Contact details, details of back-up arrangements to apply in the absence of QPPV, checklist on required practical experience/ trainings **+** A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes and This should outline the activities that are delegated and to whom, and include the access to a medically qualified person.

II. **the organizational structure of the marketing authorization holder**(clear overview of the companies) involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfillment of pharmacovigilance obligations showing the position of the QPPV in the organization/ The site(s) where the pharmacovigilance functions are undertaken / main pharmacovigilance departments / the relationship(s) between organizations and operational units relevant to the fulfillment of pharmacovigilance obligations.)

III. **the sources of safety data** (description of the main units for safety data collection)

IV. computerized systems and databases

V. **pharmacovigilance processes** (clear written description of procedures in place which must be accompanied by the list of processes for compliance management)

VI. **pharmacovigilance system performance** (The pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance./ Targets for the performance of the pharmacovigilance system shall be described and explained./ A list of performance indicators must be provided in the Annex)

VII. **Quality system** (A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance including :

- Document and Record Control for pharmacovigilance and quality system (electronic and/or hardcopy)
- Procedural documents (A general description of the types of documents used in pharmacovigilance operating procedures)
- Training (A summary description of the training concept, including a reference to the location training files, record as well as the trainings materials)
- Auditing Information about quality assurance auditing of the pharmacovigilance system

Annex to the PSMF An **annex to the pharmacovigilance system master file shall contain the following documents:**

1. A list of medicinal products covered by the pharmacovigilance system master file including the name of the medicinal product, the name of the active substance(s), and the Arab Country (ies) in which the authorization is valid
2. A list of written policies and procedures for the compliance management
3. A list of contractual agreements covering delegated activities
4. A list of tasks that have been delegated by the QPPV
5. A list of all completed audits, for a period of five years, and a list of audit schedules;
6. Where applicable, a list of performance indicators
7. Where applicable, a list of other pharmacovigilance system master files held by the same marketing authorization holder.

Operation in the Arab Countries:

Responsibilities:

I. **The applicant/marketing authorization holder** is responsible for establishing the pharmacovigilance system master file (at any marketing authorization holder or contractual partner site including the site of a contractor or marketing partner), and to submit for registering its PSMF with the national medicines authority in the national pharmacovigilance systems list/database.

II. **The national medicines authorities** are obliged to supervise the pharmacovigilance systems of marketing authorization holders so they will review the summary information about the pharmacovigilance system (& full PSMF as appropriate) included in the marketing authorization application. The full PSMF may also be requested at any time And also may be used to inform inspection planning and conduct.

A national list/database which provides a practical mechanism for maintaining up-to-date information about the MAH's or contractual partner pharmacovigilance system master file, its status, its location, the QPPV&/or LSR contact information and the products relevant to the pharmacovigilance system described in the pharmacovigilance system master file.

For the Multinational MAH/Applicant the following two documents are required (for submission requirement):

1. **The PSMF.**
2. National pharmacovigilance sub-system files **(National PSSF)** which describes the key elements of pharmacovigilance activities in the Arab County concerned.

Info to be contained in it:

a. National PSSF section on "local safety responsible (LSR)
b. National PSSF section on the "organizational structure of the MAH's local office"
c. National PSSF section on the "sources of safety data"
d. National PSSF section on "computerized systems and databases"
e. National PSSF section on "pharmacovigilance processes"
f. National PSSF section on "pharmacovigilance sub-system performance"
g. National PSSF section on "quality system"

The full PSMF (along together with its summary) and **the national PSSF** (along together with its summary) are requested to be submitted in the marketing authorization applications (i.e. pre-authorization) in the following situations:

1. The applicant has not previously held a marketing authorization in the Arab Country concerned
2. The applicant has not previously submit the PSMF and the national PSSF in the Arab Country concerned or is in the process of establishing a new pharmacovigilance system;
3. The applicant had major changes in its organization
4. The applicant has major or critical findings in the previous assessment of the pharmacovigilance system.

5. The applicant or the marketing authorization holder has a history or culture of pharmacovigilance non-compliance
6. Where specific concerns about the pharmacovigilance system(global &/or local) and/or the product safety profile exist

Except that only **a summary of the applicant's national pharmacovigilance sub-system** is required to be included in the marketing authorization application, which shall include the following elements:

- proof that the applicant has at his disposal a LSR and that he resides in the Arab Country concerned;
- the contact details of the LSR;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil on the national level the pharmacovigilance tasks and responsibilities
- A reference to the location where the national PSSF for the medicinal product is kept.

➢ The national PPSF should not routinely be submitted during the assessment of new marketing authorization applications (i.e. **pre-authorization**), but may be requested on an **ad hoc basis**,

Module III – Pharmacovigilance inspections

- In order to determine that marketing authorization holders comply with pharmacovigilance obligations established within an Arab Country, and to facilitate compliance, the national medicines authorities concerned shall conduct, pharmacovigilance inspections of marketing authorization holders.
- Shall be carried out by inspectors appointed by the national medicines authority.

The objectives of pharmacovigilance inspections are:

- to determine that the marketing authorization holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- to identify, record and address non-compliance
- to use the inspection results as a basis for enforcement action,

The national medicines authority may conduct pre-authorization inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system.

Inspection types:

system inspections	product-related inspections	Routine inspections	For cause inspections
Designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance	Focused on product-related pharmacovigilance issues, including product-specific activities and documentation.	Scheduled in advance as part of inspection programs. With no specific trigger These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance.	Undertaken when a trigger is recognized. They are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product.

For cause inspections may arise when, for example, one or more of the triggers listed below are identified:

1. **Risk-benefit balance of the product:**
   - change in the risk-benefit balance
   - delays or failure to identify or communicate a risk
   - communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the national medicines authorities
   - non-compliance or product safety issues
   - suspension or product withdrawal with no advance notice to the national medicines authorities
2. **Reporting obligations (expedited and periodic):**
   - delays or omissions in reporting;
   - poor quality or incomplete reports;
3. **Requests from the national medicines authorities:**
   - failure to provide the requested information or data within the deadline
   - poor quality or inadequate provision of data to fulfill requests for information
4. **Fulfillment of commitments.**

5. **Inspections.**
   - delays in the implementation or inappropriate implementation of corrective and preventive actions;
   - non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP)
6. **Concerns following review of the pharmacovigilance system master file.**

Pre-authorization inspections;

Are inspections performed before a marketing authorization is granted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorization application.

➢ Requested in specific circumstances:

The following aspects shall be considered during the validation phase and/or early during the assessment phase:

- The applicant has not previously operated a pharmacovigilance system
- Previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance.
- Due to product-specific safety concerns, it may be considered appropriate to examine the applicant‘s ability: - to implement product specific risk-minimization activities; or
  - To meet specific safety conditions which may be imposed or;
  - To manage routine pharmacovigilance for the product of concern

➢ In most cases, a risk assessment based on a combination of product-specific and system-related issues should be performed before a pre-authorization pharmacovigilance inspection is requested.

➢ If the outcome of the pre-authorization inspection raises concerns about the applicant‘s ability to comply with the national pharmacovigilance requirements, the following recommendations may be considered:

- Non approval of the marketing authorization;
- A **re-inspection** prior to approval of the marketing authorization
- Granting of the marketing authorization with the recommendation to perform an early post-authorization pharmacovigilance inspection.
- Imposition of safety conditions to the marketing authorization.

A **re-inspection** may be conducted on a routine basis as part of a routine inspection program & Risk factors will be assessed in order to prioritize re-inspections.

Early re-inspection may take place where:

1. Significant non-compliance has been identified
2. To verify actions taken to address findings and to evaluate ongoing compliance with the obligations

Post-authorization Pharmacovigilance inspections are inspections performed after a marketing authorization is granted and are intended to examine whether the marketing authorization holder complies with its pharmacovigilance obligations.

Remote inspections are pharmacovigilance inspections performed by inspector's remote using Communication mechanisms.

Inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection.

Factors which may be taken into consideration by the national medicines authorities when establishing pharmacovigilance inspection programs include:

1. Inspection related:
   - Compliance history
   - Re-inspection date recommended by the inspectors or assessors as a result of a previous Inspection;
2. Product related:
   - Product with additional pharmacovigilance activities or risk-minimization activities;
   - Authorization with conditions associated with safety, e.g. requirement for post-authorization Safety studies (PASS)
   - Product with large sales volume,
   - Product with limited alternative in the market place
3. Marketing authorization holder (MAH) related:
   - MAH with no previous marketing authorizations in the Arab Country concerned;
   - Negative information and/or safety concerns raised by the national medicines authority
   - Changes in the MAH organization, such as mergers and acquisitions;
   - MAH that has never been subject to a pharmacovigilance inspection;
   - MAH with many products on the market in the Arab Country concerned;
   - Resources available to MAH for the pharmacovigilance activities they undertake;
4. Pharmacovigilance system related:
   - Marketing authorization holder with sub-contracted pharmacovigilance activities
   - Change of QPPV/local safety responsible (LSR) since the last inspection
   - Changes to the pharmacovigilance safety database(s)
   - Changes in contractual arrangements
   - Delegation or transfer of pharmacovigilance system master file management.

Inspection process:

Sharing of information >>> inspection planning >>> pre-authorisation inspections >>> coordination >>> preparation >>> Conduct >>> reporting >>> *follow-up* (When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed) >>> communication and prioritization of inspections and findings.

Regulatory actions and sanctions:

According to the national legislations and regulations, in order to protect public health, the national medicines authorities are obliged to ensure compliance with PV obligations and the necessary action will be judged on a case-by-case basis.

In the event of non-compliance, possible regulatory options include the following:

- Summaries the identified non-compliances for corrective and preventive actions
- Provision of information to other medicines authorities
- Inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved
- Warning letter, non-compliance statement or infringement notice
- Making public a list of marketing authorization holders found to be seriously or persistently non-compliant
- Product recalls e.g. where important safety warnings have been omitted from product information
- Amendments or suspension of clinical trials due to product-specific safety issues
- Administrative penalties
- Referral for criminal prosecution with the possibility of imprisonment

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by the national medicines authority should be officials of, or appointed by, the national medicines authority in accordance with national regulation based upon their experience (especially in pharmacovigilance) and should undergo training.

Operation of pharmacovigilance inspections in Arab Countries:

<table>
<tr><th>Role of the national medicines authorities</th><th>Role of the Marketing Authorization Holders and Applicants</th></tr>
<tr><td>
1. establish the legal and administrative framework within which pharmacovigilance inspections operate
2. provide sufficient resources and appoint adequately qualified inspectors
3. responsible for the planning and coordination of pharmacovigilance inspections
4. Priorities the inspections in its program.
<table>
<tr><th>Inspection Programs</th><th>Cooperation and Sharing of information</th></tr>
<tr><td>A program for routine inspections for authorized products in an Arab Country will be determined.
As a general approach, a marketing authorization holder should be inspected on the basis of risk-based considerations, but it is recommended to routinely inspect MAH at least once every 4 years.</td><td>1. Training
2. Joint PV inspection
3. Exchange of info</td></tr>
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</td><td>
1. Always to be inspection-ready
2. maintain and make available to the inspectors on request, no later than 14 days after the receipt of a request, the PSMF
3. To ensure that the sites selected for inspection agree to be inspected
4. To make available to the inspectors any information and/or documentation required for the preparation of the inspection
5. To ensure that relevant staff involved in pharmacovigilance activities are present and available
6. To ensure that relevant pharmacovigilance data is accessible
7. To ensure that appropriate and timely corrective and preventive action plans are implemented with appropriate prioritization of critical and/or major findings.
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Module IV – Pharmacovigilance audits

The risk-based approach to pharmacovigilance audits is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome.

Strategic level audit planning how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years

- The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system
- resulting in an audit strategy (long term approach), which should be endorsed by upper management

Tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme

- An audit programme is a set of one or more audits planned for a specific timeframe & should be prepared in line with the long term audit strategy
- The risk-based audit programme should be based on an appropriate risk assessment
- The audit programme documentation should include a brief description of the plan for each audit to be delivered

Operational level audit planning and reporting resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system

- Planning & Fieldwork
- Reporting
- Actions based on audit outcomes & follow-up of audits