Central Administration of Pharmceutical care
General Administration for Pharmceutical Vigilance

Guideline on Good Pharmacovigilance Practice (GVP) in Egypt For Pharmaceutical Products

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Preface:

This document provides guidance on the application of good pharmacovigilance practice in the Arab Republic of Egypt. It represents the second version of the Egyptian regulations for good pharmacovigilance practices. The legal framework for pharmacovigilance of pharmaceutical products for human use, including biological products, in Egypt is given in ministerial decree 368/2012. This guideline is intended to facilitate the performance of pharmacovigilance activities in Egypt and applies on marketing authorization holders. The Egyptian Drug Authority (EDA) has a core role in coordinating these activities. Additionally, the Egyptian legislations imposes responsibility for pharmacovigilance, together with specific obligations (i.e. in terms of tasks and responsibilities), on marketing authorization holders.

This guideline is based on the European guidelines for good pharmacovigilance practices, this does NOT undermine the right of EDA to have additional or sometimes changed requirements. Multinational marketing authorization holders shall be attentive to these national requirements and bring the attention of their headquarters to them, consequently, take the necessary measure to comply.

For the operational procedures and communication with EDA, kindly follow the “Administrative manual for PV in Egypt”

Pharmacovigilance has been defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem. This guideline consists of several chapters that are major pharmacovigilance processes that are drawn up to implement the good pharmacovigilance practices in Egypt.

For healthcare workers, who play crucial role in detecting and reporting adverse events can follow the Egyptian guidelines for detecting and reporting adverse reaction by EDA Here

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1. Pharmacovigilance systems and their quality System

1.1. Introduction

This Chapter contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorization holders and EDA. How the systems of these organizations interact while undertaking specific pharmacovigilance processes is described in each respective Chapter of GVP.

The definition of a pharmacovigilance system is a system used by the marketing authorization holder and by EDA to fulfill the tasks and responsibilities and designed to monitor the safety of authorized pharmaceutical products and detect any change to their risk-benefit balance.

By following the overall quality objectives in 1.2.4. and the guiding principle in 1.2.5. to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system shall be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each pharmaceutical product covered by a quality system.

1.2. Structures and processes

1.2.1. Pharmacovigilance system

A pharmacovigilance system is defined as a system used by an organization to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized pharmaceutical products and detect any change to their risk-benefit balance.

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

1.2.2. Quality system requirements and objectives

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

In general terms, quality is a matter of level and can be measured. Measuring if the required level of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under 1.2.4.

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

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.

1.2.3. Quality cycle

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

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

1.2.4. Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

- Complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- Preventing harm from adverse reactions in humans arising from the use of authorized pharmaceutical products within or outside the terms of marketing authorization or from occupational exposure;
- Promoting the safe and effective use of pharmaceutical products, in particular through providing timely information about the safety of pharmaceutical products to patients, healthcare professionals and the public;
- Contributing to the protection of patients and public health

1.2.5. Principles for good pharmacovigilance practices

With the aim of fulfilling the overall quality objectives in 1.2.4., the following principles shall guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines shall be met.
- Upper management shall provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All persons within the organization shall be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organization shall engage in continuous quality improvement following the quality cycle in 1.2.3.
- Resources and tasks shall be organized as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of pharmaceutical products shall be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, shall be considered for decision-making.
- Good cooperation shall be fostered between marketing authorization holders, EDA, public health organizations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

1.2.6. Responsibilities for the quality system within an organization

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities. Their responsibility shall include adherence to the principles defined in 1.2.5.

For the purpose of a systematic approach towards quality in accordance with the quality cycle (see 1.2.3.); managerial staff (i.e. staff with management responsibilities) in any organization shall be responsible for:

- Ensuring that the organization documents the quality system as described in 1.2.11;
- Ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- Ensuring that adequate resources are available and that training is provided (see 1.2.7.);
- Ensuring that suitable and sufficient premises, facilities and equipment are available (see 1.2.8.);
- Ensuring adequate compliance management (see 1.2.9.);
- Ensuring adequate record management (see 1.2.10.);
- Reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness (see 1.2.12.) and introducing corrective and preventive measures where necessary;
- Ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to pharmaceutical products within an organization; identifying and investigating concerns arising within an organization regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- Ensuring that audits are performed (see 1.2.12.).
- In relation to the management responsibilities described above, upper management within an organization shall provide leadership through:
- Motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members ‘contributions within the organization; and
- Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organization.
- Ensuring that the descriptive document of its PV system reflects the reality and the strength of its PV system, as EDA will assess the maturity of this system which has a direct impact on the PV approvals for MAH’s products during the registration and re-registration cycle.

1.2.7. Training of personnel for pharmacovigilance

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 (see 1.2.7.).

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, with continuous evaluation of effectiveness of conducted trainings.

The organization shall keep training plans and records for documenting, maintaining and developing the competences of personnel. Training plans shall be based on training needs assessment and shall be subject to monitoring.

The training shall 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 shall receive and be able to seek information about what to do if they become aware of a safety concern.

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

Adequate training shall 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 but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see 1.2.11.2.), shall be provided by the organization to their personnel.

1.2.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes.

Facilities and equipment shall include office space, information technology (IT) systems and (electronic) storage space. They shall be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see 1.2.4.) and also be available for business continuity (see 1.2.11.2.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see 1.2.11.2.) shall be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There shall be processes in place to keep awareness of the valid terminologies (see Chapter 6) in their valid versions and to keep the IT systems up-to-date accordingly.

1.2.9. Specific quality system procedures and processes

1.2.9.1.Compliance management by marketing authorization holders

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

- The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the marketing authorization holder (see Chapters 8 and 10);

- The scientific evaluation of all information on the risks of pharmaceutical products as regards patients ‘or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure (see Chapters 6, 7, 8, 9);
- The submission of accurate and verifiable data on serious and non-serious adverse reactions to EDA within the legally required time-limits (see Chapters 6 and 8);
- The quality, integrity and completeness of the information submitted on the risks of pharmaceutical products, including processes to avoid duplicate submissions and to validate signals (see Chapters 5, 6,7,8 and 9);
- Effective communication by the marketing authorization holder with EDA, including communication on new or changed risks, the pharmacovigilance system master file (see Chapter 2), risk management systems (see Chapter 5), risk minimizations measures (see Chapters 5 and 12), periodic safety update reports (see Chapter 7), corrective and preventive actions (see Chapters 2, 3 and 4) and post-authorization safety studies (see Chapter 9);
- The update of product information by the marketing authorization holder in the light of scientific knowledge (see Chapter 12);
- Appropriate communication of relevant safety information to healthcare professionals and patients (see Chapter 10).

1.2.9.2.Compliance management by EDA

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

- Ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;
- Ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines;
- Ensuring independence in the performance of pharmacovigilance activities;
- Ensuring effective communication with patients, healthcare professionals, marketing authorization holders and the general public;
- Conducting inspections, based on a risk-based approach;
- Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on pharmaceutical products shall be taken in the sole interest of patients ‘and public health.

1.2.10. 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.

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

The record management system shall 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 pharmaceutical products, in accordance with the applicable retention periods.

In addition, marketing authorization holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

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

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

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

1.2.11. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

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

In order to have a systematic approach, the organization shall define in advance:

- Quality objectives specific to their organizations in accordance with the overall quality objectives provided under 1.2.4. and the structure- and process-specific quality objectives in accordance with each Chapter of GVP; and
- Methods for monitoring the effectiveness of the pharmacovigilance system (see 1.2.12.).

The quality system shall be documented by:

- Documents on organizational structures and assignments of tasks to personnel (see 1.2.11.1.);
- Training plans and records (see 1.2.7.);

- Instructions for the compliance management processes (see 1.2.9.);
- Appropriate instructions on the processes to be used in case of urgency, including business continuity (see 1.2.11.2.)
- Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities
- Reports of quality audits and follow-up audits, including their dates and results.

Training plans and records shall be kept and made available for audit and inspection.

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

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

1.2.11.1. Additional quality system documentation by marketing authorization holders

In addition to the quality system documentation in accordance with 1.2.11., marketing authorization holders shall document:

- Their human resource management in the pharmacovigilance system master file (PSMF) (see Chapter 2)
- Job descriptions defining the duties of the managerial and supervisory staff.
- An organizational chart defining the hierarchical relationships of managerial and supervisory staff.
- Instructions on critical processes (see 1.2.11.2.) in the pharmacovigilance system master file (PSMF) (see Chapter 2); and
- Their record management system in the pharmacovigilance system master file (PSMF) (see Chapter 2).

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

For the requirements of documenting the quality system in the pharmacovigilance system master file (PSMF) or its annexes, see Chapter 2.

1.2.11.2. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes shall be considered as critical include:

- Continuous safety profile monitoring and benefit-risk evaluation of authorized pharmaceutical products; establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;
- Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- Signal management;
- Scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- Meeting commitments and responding to requests from EDA, including provision of correct and complete information;
- Interaction between the pharmacovigilance and product quality defect systems;
- Communication about safety concerns between marketing authorization holders and EDA, in particular notifying changes to the risk-benefit balance of pharmaceutical products;
- Communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of pharmaceutical products;
- Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from EDA.
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required.
- Business continuity plans shall be established in a risk-based manner and shall include:
- Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- Back-up systems for urgent exchange of information within an organization, amongst organizations sharing pharmacovigilance tasks as well as between marketing authorization holders and EDA.
- Collection and management of any product Quality complain with reflection of reporting timelines (in case MAH/concerned MAH the manufacturing site).

1.2.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

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

- Reviews of the systems by those responsible for management;
- Audits;
- Compliance monitoring;
- Inspections;
- Evaluating the effectiveness of actions taken with pharmaceutical products for the purpose of minimizing risks and supporting their safe and effective use in patients.

The organization may use performance indicators to continuously monitor the good performance of pharmacovigilance activities in relation to the quality requirements. The quality requirements for each pharmacovigilance process are provided in each Chapter of Egypt GVP as appropriate.

The requirements for the quality system itself are laid out in this Chapter and its effectiveness shall be monitored by managerial staff, who shall review the documentation of the quality system (see 1.2.11.) at regular intervals, with the frequency and the extent of the reviews to be determined in a risk-based manner. Pre-defined programs for the review of the system shall therefore, be in place. Reviews of the quality system shall include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness. Audits of the quality system shall include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in Chapter 4. In relation to the pharmacovigilance system of a marketing authorization holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited. The report shall include the results of audits of organizations or persons the marketing authorization holder has delegated tasks to, as these are part of the marketing authorization holders' pharmacovigilance system.

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures shall be implemented when deemed necessary. In particular, as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. Additionally, EDA shall have in place arrangements for monitoring the compliance of marketing authorizations holders with legally required pharmacovigilance tasks and responsibilities. They shall further ensure compliance with the legal requirements by means of conducting inspections of marketing authorization holders (see Chapter 3). Guidance on compliance monitoring for each pharmacovigilance process is provided in each Chapter of GVP as appropriate.

Requirements and methods for evaluating the effectiveness of actions taken upon pharmaceutical products for the purpose of minimizing risks and supporting the safe and effective use of medicines in patients are described in Chapter 12.

1.2.13. Crisis prevention and management

A Crisis is any event that comes to public notice and threatens the health or safety of individuals or groups. Crises usually erupt suddenly and dramatically; they require rapid and effective response and communications. For crisis prevention and management see section 1.3.3.

1.2.14. Preparedness planning for pharmacovigilance in public health emergencies

Any pharmacovigilance system shall be adaptable to public health emergencies and preparedness plans shall be developed as appropriate. For preparedness planning in Egypt, see 1.3.4.

1.3. Operation in Egypt

1.3.1. Overall pharmacovigilance responsibilities of the applicant and marketing authorization holder in Egypt

The marketing authorization holder in Egypt is responsible for the respective pharmacovigilance tasks and responsibilities in order to assure responsibility and liability for its authorized pharmaceutical products and to ensure that appropriate action can be taken, when necessary.

For this purpose, the marketing authorization holder shall operate a pharmacovigilance system and shall establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities.

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

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorization in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorization holder for all authorized pharmaceutical products (see Chapter 2). The applicant or the marketing authorization holder is also responsible for developing and maintaining product-specific risk management systems (see Chapter 5).

Guidance on the structures and processes on how the marketing authorization holder shall conduct the pharmacovigilance tasks and responsibilities is provided in the respective Egypt GVP Chapters.

1.3.1.1.Responsibilities of the marketing authorization holder in relation to the qualified person responsible for pharmacovigilance in Egypt

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) for local MAHs, and for multinational MAHs a Local Safety Responsible (LSR) located in Egypt.

The marketing authorization holder shall submit the name and contact details of the QPPV/LSR to EDA. Changes to this information shall be submitted immediately to EDA as a nomination and de-nomination letters.

The QPPV/LSR position is a fulltime job. The duties of the QPPV/LSR shall be defined in a job description. The appointed person shall be **fully dedicated** to his job as a QPPV/LSR. The hierarchical relationship of the QPPV/LSR shall be defined in an organizational chart together with those of other managerial and supervisory staff (QPPV/LSR shall report directly to CEO/General Manager/Medical director)

Information relating to the QPPV shall be included in the pharmacovigilance systems master file (PSMF) (see Chapter 2).

Each Pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one marketing authorization holder (i.e. only in case of subcontracting to a third party organization), for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorization holder, provided that the QPPV is able to fulfil all obligations.

<u>For multinational companies:</u>

In addition to the headquarter QPPV, EDA requests the nomination of a pharmacovigilance contact person (local safety responsible) in Egypt. Reporting in this context relates to pharmacovigilance tasks and responsibilities, and not to line management.

The marketing authorization holder shall ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorization holder. The marketing authorization holder shall therefore ensure that the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it in accordance with the guideline. The authority over the pharmacovigilance system and the PSMF shall allow the QPPV to implement changes to the system and to provide input into risk management plans as well as into the preparation of regulatory action in response to emerging safety concerns.

Overall, the marketing authorization holder shall ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed in 1.3.1.3. In order to do this, the marketing authorization holder shall ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:

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

The outcome of the regular reviews of the quality system referred to in 1.2.6. and 1.2.12. and the measures introduced shall be communicated by the managerial staff to the QPPV.

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

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

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

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

When a marketing 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, the QPPV shall be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see 1.3.1.5.) so that all necessary provisions relevant to the pharmacovigilance system are included.

1.3.1.2.Qualifications of the qualified person responsible for pharmacovigilance in Egypt

The marketing authorization holder shall ensure that the QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPVs shall have a minimum of bachelor degree of pharmacy or medicine, basic training in epidemiology and biostatics.

In addition; they shall have the skill for the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences as well as epidemiology and biostatistics.

The expectation is that the applicant or marketing authorization holder will assess the qualification of the QPPV prior to appointment by, for example, reviewing university qualifications, knowledge of national pharmacovigilance requirements and pharmacovigilance experience. **(**It is accepted by EDA that for only a transitional period**,** the QPPV qualifications may be expressed in terms of his pharmacovigilance training rather than his practical experience in pharmacovigilance. Under these circumstances, once the QPPV is appointed, the MAH is responsible of providing him the unachieved trainings in light of the checklist in chapter II). (Consult with EDA for transitional period duration & conditions, if any,)

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

1.3.1.3.Role of the qualified person responsible for pharmacovigilance in Egypt

The qualified person responsible for pharmacovigilance (QPPV) is a natural person.

The QPPV appointed by the marketing authorization holder shall be appropriately qualified (see 1.3.1.2.) and shall be at the marketing authorization holder`s disposal permanently and continuously back-up procedures in the case of absence of the QPPV shall be in place, and shall

be accessible through the QPPV ‘s contact details. The QPPV shall ensure that the back-up person has all necessary information to fulfil the role.

The QPPV shall be responsible for the establishment and maintenance of the marketing 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. Hence, the QPPV shall have access to the pharmacovigilance system master file (PSMF) (see Chapter 2) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV ‘s responsibility.

In relation to the pharmaceutical products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV shall include: having an overview of pharmaceutical product safety profiles and any emerging safety concerns;

- Having awareness of any conditions or obligations adopted as part of the marketing authorizations and other commitments relating to safety or the safe use of the products;
- Having awareness of risk minimization measures;
- Being aware of and having sufficient authority over the content of risk management plans;
- Being involved in the review and sign-off of protocols of post-authorization safety studies conducted in Egypt or pursuant to a risk management plan agreed in Egypt;
- Having awareness of post-authorization safety studies requested by EDA including the results of such studies;
- Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the national legal requirements and GVP in Egypt;
- Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to EDA;
- Ensuring a full and prompt response to any request from EDA for the provision of additional information necessary for the benefit-risk evaluation of a pharmaceutical product;
- Providing any other information relevant to the benefit-risk evaluation to EDA;
- Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);
- The QPPV or the LSR shall acting as a single pharmacovigilance contact point for EDA on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

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

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

1.3.1.4.Specific quality system processes of the marketing authorization holder in Egypt

In applying the requirements set out in 1.2.9.1. in Egypt, the marketing authorization holder shall put in place the following additional specific quality system processes for ensuring:

- The submission of adverse reaction data to National Pharmacovigilance Center/ Directorate within the legal timelines;
- The monitoring of the use of terminology either systematically or by regular random evaluation;
- The retention of minimum elements of the pharmacovigilance system master file (PSMF) (see Chapter 2) as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the marketing authorization holder;

The retention of pharmacovigilance data and documents relating to individual authorized pharmaceutical products as long as the marketing authorization exists and for at least further 10 years after the marketing authorization has ceased to exist;

The retention of ICSRs shall be lifelong.

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

Documents transferred in situations where the business of the marketing authorization holder is taken over by another organization shall be complete.

Use of internationally agreed terminology, For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and pharmaceutical product information, marketing authorization holders and EDA shall apply the following terminology:

the Medical Dictionary for Regulatory Activities (MedDRA) as developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), multidisciplinary topic M1;

the terminology set out in EN ISO 11615:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, Data elements and structures for unique identification and exchange of regulated **pharmaceutical product information'** (ISO/FDIS 11615:2012);

the terminology set out in EN ISO 11616:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, Data elements and structures for unique identification and exchange of regulated **pharmaceutical product information'** (ISO/FDIS 11616:2012);

the terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, Data elements and structures for unique identification and exchange of regulated **information on substances'** (ISO/FDIS11238:2012);

the terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, Data elements and structures for unique identification and exchange of regulated information on **pharmaceutical dose forms, units of presentation and routes of administration** '(ISO/FDIS 11239:2012);

the terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, Data elements and structures for unique identification and exchange of **units of measurement** '(ISO/FDIS 11240:2012).

1.3.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorization holder

The marketing authorization holder may subcontract certain activities of the pharmacovigilance system to third parties, i.e. to a PV service provider organization "**not individuals**, **the freelance person is not applicable in Egypt**. This may include the role of the QPPV. The marketing authorization holder shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF) (see Chapter 2). The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorization holder.

Where a marketing authorization holder has subcontracted some tasks of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks. All guidance provided in Egypt GVP is also applicable to the other organization to which the tasks have been subcontracted.

When subcontracting tasks to a PV service provider organization, the marketing authorization holder shall draw up subcontracts and these shall be detailed, up-to-date and clearly document the contractual arrangements between the marketing authorization holder and the other organization, describing arrangements for delegation and the responsibilities of each party. A description of the subcontracted activities and/or services shall be included in the PSMF and a list of the subcontracts shall be included in an annex to the PSMF, specifying the product(s) concerned (see Chapter 2).

The other organization may be subject to inspection at the discretion of EDA.

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

For responsibilities of the MAH towards the QPPV in this context, see 1.3.1.1.

1.3.2. Overall pharmacovigilance responsibilities within Egypt

EDA is responsible for the respective pharmacovigilance tasks and responsibilities in order to ensure that appropriate action can be taken, when necessary. For this purpose, EDA, represented by the general administration of pharmaceutical vigilance shall operate a pharmacovigilance system and shall establish and use an adequate and effective quality system for performing their pharmacovigilance activities.

1.3.2.1.Role of EDA

EDA shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks. In this context, EDA is responsible for the safety monitoring of each pharmaceutical product. In particular, EDA shall be responsible for monitoring data originating in their territory. EDA is responsible for granting, varying, suspending and revoking a marketing authorization. The pharmacovigilance tasks and responsibilities of EDA for each process in relation to such products, are detailed in the respective Chapters of Egypt GVP.

EDA shall monitor the compliance of the marketing authorization holder with national legal pharmacovigilance requirements.

1.3.2.2.Role of the national Pharmacovigilance Committee

The role of the national Pharmacovigilance committee is to provide advice on the safety of pharmaceutical 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 phases leading to recommendations on action at the request of the pharmaceutical vigilance general administration for products available in Egypt. The roles and responsibilities of the national Pharmacovigilance Committee include but not limited to the following:

Evaluation of potential signals arising from spontaneous reporting, including those identified from National Pharmacovigilance and safety reports database, and all other sources

Investigation of adverse reactions, if required.

Regularly review Drug monitor of safety concerns, when needed.

Discussion of emerging safety concerns, if required.

Discussion of PSURs, if required.

Recommendations on Risk-benefit evaluations and actions necessary to minimize risk and maximize benefit.

1.3.2.3.Specific quality system processes of the quality system of EDA in Egypt

EDA shall put in place the following additional specific quality system processes for:

- Monitoring and validating the use of terminology 4, either systematically or by regular random evaluation; assessing and processing pharmacovigilance data in accordance with the timelines provided by EDA;
- Arranging for the essential documents describing their pharmacovigilance systems to be kept as long as the system exists and for at least further 5 years after they have been formally terminated;

- Ensuring that pharmacovigilance data and documents relating to individual authorized pharmaceutical products are retained as long as the marketing authorization exists or for at least further 10 years after the marketing authorization has expired.

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

The retention periods above apply unless the documents shall be retained for a longer period where national law so requires.

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

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

In addition to the above, EDA shall establish procedures for collecting and recording all suspected adverse reactions that occur in Egypt. (see Chapter 6).

In addition, EDA shall establish procedures for literature monitoring. In addition to the quality system documentation in accordance with 1.2.11., EDA shall clearly determine, and to the extent necessary, keep accessible the organizational structures and the distribution of tasks and responsibilities.

Quality audits of EDA pharmacovigilance systems (see 1.2.12.) shall be performed according to a common methodology.

1.3.3 Crisis prevention and management

Crisis prevention

Prevention of safety crisis has three main aspects. Firstly, having a pharmacovigilance system that is functioning proactively in terms of Risk management plans` implementation as well as data collection, management, analysis, and communications.
Secondly, a high state of alert for early, maybe weak signals of problems: a handful of ADR reports; a newspaper report of patient injury; new safety concerns emerging in another country; unexplained failure of treatment; anything that could escalate over time into a major crisis.
Lastly, is reputation. An organization that has open communications with its audiences, conscientiously explains what it is doing at all times, is known and trusted, will suffer far less in crisis than one that is regarded as remote and secretive.

Crisis management

- Management of a crisis requires not only resolution of the crisis event, but also very skilled management of the often intense emotions and outrage that the public may feel.
- A sudden batch of unexpected and serious ADRs
- This is one of the commonest causes of crisis in pharmacovigilance for which every PV center shall plan. The issues and relationships and communications are more complex than in the case of fires, but the basic crisis management process is exactly the same:
- Identify the risk: unexpected injury to patients and public outrage

- Assess the risk: probable and serious
- Initiate preventive measures: a constant state of high alert and attention for any evidence or allegation, however seemingly weak, from any source, of unexpected injury or death or other problems
- Establish procedures for rapid investigation, review, analysis and decision-making about problems, and for communication with all stakeholders (this may require, for example, immediate access to pre-designated technical experts to be sent out into the field).
- Review and rehearse procedures prior to crisis erupting

1.3.4 Preparedness planning for pharmacovigilance in public health emergencies in Egypt

The pharmacovigilance systems of marketing authorization holders, and EDA in Egypt shall be adaptable to public health emergencies. Preparedness plans shall be developed as appropriate (see 1.2.13.).

A public health emergency is a public health threat duly recognized either by the World Health Organization (WHO) or EDA.

Pharmacovigilance requirements for public health emergencies shall be considered by EDA on a case-by-case basis and appropriately notified to marketing authorization holders and the public. EDA publish their notifications on their websites.

2. Pharmacovigilance Master File

2.1. Introduction

It is legally required by the marketing authorization holders (MAHs) to maintain and make available upon request a pharmacovigilance system master file (PSMF) to strengthen the conduct of pharmacovigilance activities in Egypt.

The pharmacovigilance system master file definition is a detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized pharmaceutical products.

The pharmacovigilance system master file shall be located either at the site where the main pharmacovigilance activities of the marketing authorization holder are performed or at the site where the qualified person responsible for pharmacovigilance operates.

It is a requirement of the marketing authorization application that summary information about the pharmacovigilance system is submitted to EDA. This summary includes information on the location of the pharmacovigilance system master file (see 2.2.2.1).

There is no requirement for variations for changes in the content of the pharmacovigilance system master file.

This Chapter provides detailed guidance regarding the requirements for the pharmacovigilance system master file, including its maintenance, content and associated submissions to EDA.

Special considerations for multinational MAHs/ applicant are provided in 2.3.3.

For the multinational MAHs/applicants in Egypt:

All MAHs shall have an appropriate system of pharmacovigilance in place, the Pharmacovigilance activities in Egypt concerned functions as a part or sub-system of its global pharmacovigilance system and integrate with it, the content of the pharmacovigilance system master file shall reflect **global availability** of safety information for pharmaceutical products authorized for the MAH, with information on the pharmacovigilance system to the local or regional activities. The Multinational MAHs/Applicants shall provide clear illustration of the key elements of both global pharmacovigilance system and national pharmacovigilance sub-system, highlighting the role of LSR, which pharmacovigilance activities are carried out in Egypt, which are carried out in the headquarter/globally and how they integrate together.

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

The PSMF (it is accepted to be according to European Good Pharmacovigilance Practice which is the base for this guideline, All the regulations that will be described in this chapter apply to the PSMF of the multinational MAH/applicant), and

National Pharmacovigilance Sub-System file (National PSSF) which describes the key elements of pharmacovigilance activities in Egypt.

2.2. Structures and processes

The pharmacovigilance system master file is a legal requirement in Egypt. This guidance concerns the requirements for the pharmacovigilance system master file and is applicable for any pharmaceutical product authorized in Egypt. The required content and management of the

pharmacovigilance system master file applies irrespective of the organizational structure of a marketing authorization holder, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV ‘s) residence, the location at which he/she carries out his/her tasks.

The content of the pharmacovigilance system master file shall reflect global availability of safety information for pharmaceutical products authorized in Egypt, with information on the pharmacovigilance system not just confined to local or regional activities.

2.2.1. Objectives

The pharmacovigilance system master file shall describe the pharmacovigilance system and support/document its compliance with the requirements. As well as fulfilling the requirements for a pharmacovigilance system master file laid down in the national legislation and guidance, it shall also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorizations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by EDA. The pharmacovigilance system master file provides an overview of the pharmacovigilance system, which may be requested and assessed by EDA during marketing authorization application(s) or post-authorization.

Through the production and maintenance of the pharmacovigilance system master file, the marketing authorization holder and the QPPV shall be able to:

- Gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
- Confirm aspects of compliance in relation to the system;
- Obtain information about deficiencies in the system, or non-compliance with the requirements;
- Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

The use of this information shall contribute to the appropriate management of and improvement(s) to the pharmacovigilance system.

The requirements for submission of a summary of the marketing authorization holder‘s pharmacovigilance system, provision of the content of pharmacovigilance system master file and the history of changes shall enable the planning and effective conduct of inspections by EDA, based on a risk assessment approach.

Responsibilities, in terms of the pharmacovigilance system master file, for marketing authorization holders and applicants, EDA are described in detail in Section C.

2.2.2. Registration and maintenance

2.2.2.1.Summary of the applicant’s pharmacovigilance system

Except in the situations described in the accessibility of PSMF/PSSF, where the full PSMF/PSSF (along together with its summary) is requested to be submitted only a summary with any nomination and denomination of PV staff, which shall include **in addition** the following elements:

The contact details and full data and information (national ID, official nomination letter, certificates, any change in PV staff ...etc.) which are required for the qualified person and all PV staff.

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
- The full contact details of the qualified person;
- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the pharmacovigilance tasks and responsibilities listed in this GVP chapters;
- A reference to the location where the pharmacovigilance system master file for the pharmaceutical product is kept.

For other products than pharmaceutical products (e.g., herbal or homeopathic pharmaceutical products, etc.), the MAHs shall follow the instruction released from EDA regarding Pharmacovigilance requirements.

2.2.2.2.Location

The pharmacovigilance system master file 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). Based on this rule, the PSMF shall be located in Egypt, an exception is in the situation where the main activities take place outside Egypt (e.g. multinational MAHs/applicants), the location shall default to the site where the QPPV operates or where the main pharmacovigilance activities are performed (e.g. located in the country of headquarter) provided that:

- The PSMF is made available to EDA at any time; and
- The local office/ affiliate of the MAH/applicant has detailed description on the pharmacovigilance system/ activities on the local level

Details about the location of the pharmacovigilance system master file are required to be notified to EDA, and any change to the location shall be notified immediately to EDA in order to have the information updated. The required location information for the PSMF is a physical office address of the marketing authorization holder or a contracted third party. Where the pharmacovigilance system master file is held in electronic form, the location stated shall be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location.

When determining the main site of pharmacovigilance activity, the marketing authorization holder shall consider the most relevant site for the pharmacovigilance system as a whole, since the relative importance of particular activities may vary according to products and fluctuate in the short term. The marketing authorization holder shall have an appropriate rationale for the location decision.

In the situation where a main site cannot be determined, the location shall default to the site where the QPPV operates.

2.2.2.3.Registration

EDA shall 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.

All pharmacovigilance system master files shall be registered at EDA in this list/database. The MAH shall submit for such registration. In addition, the MAH shall notify EDA to update the database with the location of the pharmacovigilance system master file for each product, and update the information immediately upon change.

2.2.2.4.Transfers of responsibilities for the PSMF

The pharmacovigilance system may change with time. Transfer or delegation of responsibilities and activities concerning the master file shall be documented (see 2.2.4.2. and 2.2.4.8.) and managed to ensure that the marketing authorization holders fulfil their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file shall also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that shall be routinely and promptly notified to the QPPV are:

- Updates to the pharmacovigilance system master file or its location that are notified to EDA.
- The addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits and inspections). The QPPV shall also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;
- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the pharmacovigilance system master file EDA.
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies or the addition of territories.

Any recipient QPPV shall explicitly accept the following changes in writing:

- Transfer of responsibility for a pharmacovigilance system to a QPPV.

The QPPV shall be in a position to ensure and to verify that the information contained in the pharmacovigilance system master file is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see Chapter 1).

2.2.3. The representation of pharmacovigilance systems

The pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized pharmaceutical products. It shall describe the pharmacovigilance system for one or more pharmaceutical products of the marketing authorization holder. For different categories of pharmaceutical products, the marketing authorization holder may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate pharmacovigilance system master file. Those files shall cumulatively cover all pharmaceutical products of the marketing authorization holder for which a marketing authorization has been granted.

- It is anticipated that there will be circumstances where a single marketing authorization holder may establish more than one pharmacovigilance system e.g. specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one marketing authorization holder. In either case, a single and specific pharmacovigilance system master file shall be in place to describe each system.
- A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.
- Where a pharmacovigilance system is shared by several marketing authorization holders each marketing authorization holder is responsible ensuring that a pharmacovigilance system master file exists to describe the pharmacovigilance system applicable for his products. For a particular product(s) the marketing authorization holder may delegate through written agreement (e.g. to a

  licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorization holder is responsible. In this case the pharmacovigilance system master file of the marketing authorization holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system ‘s information for the marketing authorization holder and the authorities. The marketing authorization holder shall be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the pharmacovigilance system master file in a current and accessible state can be delegated.
- Where applicable, a list of all pharmacovigilance system master files held by the same marketing authorization holder shall be provided in the annex (see 2.2.4.8.); this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).
- Submission of summary information to EDA cannot contain multiple locations for a single pharmacovigilance system master file. The address of the location of the pharmacovigilance system master file provided shall be an office address which reflects either the site where the main pharmacovigilance activities of the marketing authorization holder are performed or the site where the qualified person responsible for pharmacovigilance operates. This address may be different to that of the applicant/marketing authorization holder, for example, a different office of the marketing authorization holder or when a third party undertakes the main activities.
- Similarly, the QPPV details aligned to a product may be those of a contract QPPV responsible for the pharmacovigilance system for a particular pharmaceutical product, and not necessarily a QPPV directly employed by the marketing authorization holder.
- When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorization holder retains ultimate responsibility for the pharmacovigilance system, for ensuring submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to EDA upon request. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, shall be in place.
- In case of the termination of the PV agreement, both partners the MAH and the service provider shall inform EDA immediately according to the timelines stipulated in the internal

rules of procedures with this update, the MAH shall be responsible for monitoring the safety of its products and responsible for either to have its own PV system or outsourced another partner, and updating EDA with this update immediately.

When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own pharmacovigilance system master files. Accessibility of the pharmacovigilance system master file to all the applicable marketing authorization holder(s), and its provision to EDA shall be defined in written agreements. It is vital that marketing authorization holder(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

2.2.4. 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 shall reflect the global availability of safety information for pharmaceutical products authorized in Egypt. The content shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex headings described in 2.2.6.1. The main principle for the structure of the content of the pharmacovigilance system master file is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it shall be referred to and contained in the Annexes. The control associated with change of content is described in section 2.2.5.

It is accepted that, where no marketing authorization (and master file) previously existed in Egypt, there may be information that cannot be initially provided, for example, compliance information, however, descriptions of what will be implemented shall be provided instead.

2.2.4.1.PSMF section on qualified person responsible for pharmacovigilance (QPPV)

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

For the QPPV, contact details shall be provided in the marketing authorization application.

The information relating to the QPPV provided in the PSMF shall include:

- A description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
- A summary curriculum vita with the key information on the role of the qualified person responsible for pharmacovigilance;
- Contact details;
- Details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and

Checklist on the following required practical experience/ trainings. Once the QPPV/LSR & PV staff are appointed, the MAH is responsible of providing the unachieved trainings in light of the checklist below.

Topic	***Practical experience (insert √ or X in the respective field)***
Pharmacovigilance methods (e.g., active surveillance…etc.).	
ICSRs processing activities (including: MedDRA coding, Causality assessment, Case Narrative Writing for Reporting Adverse Events…etc.) .	
Evidence based –medicine, how to conduct literature search.	
Pharmacovigilance quality management.	
Pharmaco-epidemiology.	
Biostatistics.	
Signal detection.	
Medical Aspects of Adverse Drug Reactions	
Risk benefit assessment in Pharmacovigilance.	
National pharmacovigilance regulations.	
How to prepare PBRER	
Pharmacovigilance Planning and Risk Management Plans.	
How to prepare PSMF.	
Risk communication, DHPC.	

During the transitional period: add 3rd column to highlight the trainings; the table header will be as follow (insert √ or X in the respective field):

Topic	***Practical experience***	***Training***

For multinational MAH/ applicant; information relating to the contact person for pharmacovigilance (local safety responsible, LSR) nominated at national level, including contact details.

A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes (see 2.2.4.8.). This shall outline the activities that are delegated and to whom, and include the access to a medically qualified person if applicable. This list may be supplied as a copy of a written procedural document provided the required content is covered.

The details provided in relation to the QPPV shall also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied shall include name, postal, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorization holder address.

If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorization holder, this shall be indicated and the name of the company the QPPV works for provided.

2.2.4.2.PSMF section on the organizational structure of the marketing authorization holder

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

A description of the organizational structure of the marketing authorization holder relevant to the pharmacovigilance system shall be provided. The description shall provide a clear overview of the company (ies) involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations. This shall include third parties. Specifically, the pharmacovigilance system master file shall describe:

The organizational structure of the marketing authorization holder(s), showing the position of the QPPV in the organization.

The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorization study management, and management of safety variations. Diagrams may be particularly useful; the name of the department or third party shall be indicated.

Delegated activities

The pharmacovigilance system master file, where applicable, shall contain a description of the delegated activities and/or services relating to the fulfillment of pharmacovigilance obligations. This includes arrangements with other parties in any country, worldwide and if applicable, to the pharmacovigilance system applied to products authorized in Egypt.

Links with other organizations, such as co-marketing agreements and contracting of pharmacovigilance activities shall be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations shall be provided. This may be in the form of a **list/table** to show the parties involved, the roles undertaken and the concerned product(s) and territories.

The list shall be organized according to; service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.), commercial arrangements (Manufacturing, distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.). Individual contractual agreements shall be annexed with the PSMF when the latter is submitted. Individual contractual agreements shall be made available at the request of EDA at any time or during inspection and audit and the list provided in the Annexes (see 2.2.4.8.).

*2.2.4.3.*PSMF section on the sources of safety data

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

The description of the main units for safety data collection shall include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in Egypt. This shall include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the pharmacovigilance system master file. Information about third parties (license partners or local distribution/marketing arrangements) shall also be included in the section describing contracts and agreements (see 2.2.4.2. and 2.2.4.8.).

Description supported by **Flow diagrams** shall be used to indicate the main stages, timeframes and parties involved. However, represented, the description of the process for ICSRs from collection to reporting to EDA shall indicate the departments and/or third parties involved.

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programs sponsored by the marketing authorization holder through which ICSRs could be reported. MAHs shall be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight. It is recommended that the list shall be comprehensive for products authorized in Egypt, irrespective of indication, product presentation or route of administration. The list shall describe, on a worldwide basis, the status of each study/program, the applicable country (ies), the product(s) and the main objective. It shall distinguish between interventional and non-interventional studies and shall be organized per active substance. The list shall be comprehensive for all studies/programs and shall include ongoing studies/programs as well as studies/programs completed in the last two years and may be located in an Annex or provided separately.

2.2.4.4.PSMF section on computerized systems and databases

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the pharmacovigilance system master file.

Where multiple computerized systems/databases are used, the applicability of these to pharmacovigilance activities shall be described in such a way that a clear overview of the extent of computerization within the pharmacovigilance system can be understood. The validation status of key aspects of computer system functionality shall also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance shall be included in summary, and the nature of the documentation available described. For non-electronic systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, shall be described.

It is understood that for multinational MAH this global safety database might be located outside Egypt (at the site where the main pharmacovigilance activities are performed globally e.g. Headquarter). However, LSR shall have online access to national safety cases and all national

pharmacovigilance data of Egypt; otherwise at least backup database of this national data shall always be kept in the local office.

2.2.4.5.PSMF section on pharmacovigilance processes

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

An essential element of any pharmacovigilance system is that there are clear written procedures in place. Chapter 1 describes the required minimum set of written procedures for pharmacovigilance. A **description** of the procedural documentation available (standard operating procedures, manuals, at a global and/or national level etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) shall be provided in the pharmacovigilance system master file.

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

- Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this shall include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
- Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions shall be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area shall clarify what are local and what are global activities;
- PSUR scheduling, production and submission, (see Chapter 7);
- Communication of safety concerns to consumers, healthcare professionals and EDA;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures shall cover both internal and external communications.

In each area, the marketing authorization holder shall be able to provide **evidence** of a system that supports appropriate and timely decision making and action.

The description shall be accompanied by the **list** of the following **processes for compliance management**, as well as interfaces with other functions: the continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and appropriate measures are taken by the marketing authorization holder; the scientific evaluation by the marketing authorization holder of all information on the risks of pharmaceutical products; the submission of accurate and verifiable data on serious and non-serious adverse reactions to EDA within the time limits; the quality, integrity and completeness of the information submitted on the risks of pharmaceutical products, including processes to avoid duplicate submissions and to validate signals; effective communication by the marketing authorization holder with EDA, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions, and post-authorization studies; the update of product information by the marketing authorization holder in the light of scientific knowledge, and on the

basis of a continuous monitoring by the marketing authorization holder of information released by EDA; appropriate communication by the marketing authorization holder of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to EDA requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, shall comprise **in cross matching** with each one of the topics highlighted above in this section the topic name, procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties shall be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this shall be indicated (and the names of the applicable countries provided).

2.2.4.6.PSMF section on pharmacovigilance system performance

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

The pharmacovigilance system master file shall contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file shall include a description of the monitoring methods applied and contain as a minimum:

An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs shall be provided to show the timeliness of 15-day and 90-day reporting over the past year;

A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This shall include information provided by EDA regarding the quality of ICSR reporting, PSURs or other submissions;

An overview of the timeliness of PSUR reporting to EDA (the annex shall reflect the latest figures used by the marketing authorization holder to assess compliance);

An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and EDA deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;

Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and explained (the accepted target is not less than 90%, and it is expected to be improved by time). A list of performance indicators shall be provided in the Annex to the pharmacovigilance system master file, alongside the results of (actual) performance measurements.

Any deviation or non-compliance which is detected either by the MAH or by Pharmaceutical Vigilance General Administration shall be mentioned and justified, and the appropriate corrective and preventive actions shall be taken and described in the pharmacovigilance master file.

2.2.4.7.PSMF section on quality system

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

A description of the quality management system shall be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance. This shall include:

Document and Record Control

Provide a description of the archiving arrangements for electronic and/or hardcopy versions of the different types records and documents for pharmacovigilance and quality system (see also Chapter 1)

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc.), the applicability of the various documents at global, regional or local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.
- Information about the documentation systems applied to relevant procedural documents under the control of third parties.
- A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed shall be provided, and the detailed guidance for the inclusion of these is in section 2.2.4.5.

Training

Staff shall be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.

Training shall be done in accordance to a training plan, and this training plan shall be provided on the related section within the pharmacovigilance master file.

- A description of the resource management for the performance of pharmacovigilance activities: the organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organizational structure (see 2.2.4.2)
- Information about sites where the personnel are located (this is described under sections 2.2.4.2 and 2.2.4.3) whereby the sites are provided in the PSMF in relation to the organization of specific pharmacovigilance activities and in the Annexes which provide the list of site contacts for sources of safety data. However, a description shall be provided in order to explain the training organization in relation to the personnel and site information;
- 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 shall be included in the pharmacovigilance system master file. A description of the risk-based approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines shall be

provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to 2.2.4.8. This list shall describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the pharmacovigilance obligations, and cover a rolling 5-year period.

The pharmacovigilance system master file shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the national criteria for major or critical findings shall be indicated (see Chapter 4). The audit report shall be documented within the quality system; in the pharmacovigilance system master file it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, shall be identified. The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes shall therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the pharmacovigilance system master file shall also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

Audit report or any audit related information shall be ready for the authority’s request at any time either within the PSMF or for inspection.

2.2.4.8.Annex to the PSMF

Remember that for Multinational MAHs the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

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

- A list of pharmaceutical products covered by the pharmacovigilance system master file including the name of the pharmaceutical product, the name of the active substance(s), and the Country (ies) in which the authorization is valid;
- The list of pharmaceutical products authorized in Egypt shall also include the authorization number(s) including:

The name of the pharmaceutical product,
The name of the active substance(s),
Dosage form
Concentration
The authorization number in Egypt,

The presence on the market in Egypt stated in the list (marketing status);
Other countries where the product is authorized or on the market.
The list shall be organized per active substance and, where applicable, shall indicate what type of product specific safety monitoring requirements exists (for example risk minimization measures contained in the risk management plan (for global MAHs national display of RMP) or laid down as conditions of the marketing authorization, non-standard PSUR periodicity. The monitoring information may be provided as a secondary list.

For marketing authorizations that are included in a different pharmacovigilance system; for example, because the MAH has more than one pharmacovigilance system (for multinational MAHs on national level) or third party agreements exist to delegate the system, reference to the additional pharmacovigilance system master file(s) shall also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of pharmacovigilance system master files.

Where pharmacovigilance systems are shared, all products that utilize the pharmacovigilance system shall be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the compliance management (see 2.2.4.5.);
- A list of contractual agreements covering delegated activities including the pharmaceutical products and territory (ies) concerned. In addition, a copy of the individual contractual agreements relevant to Egypt shall also be included in this annex when the PSMF is submitted to EDA;
- A list of tasks that have been delegated by the qualified person for pharmacovigilance;
- A list of all completed audits, for a period of five years, and a list of audit schedules;
- Where applicable, a list of performance indicators (see 2.2.4.6.);
- Where applicable, a list of other pharmacovigilance system master files held by the same marketing authorization holder;

This list shall include PSMF/PSSF number(s), and the name of MAH of the QPPV/LSR responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not a marketing authorization holder, the name of the service provider shall also be included.

A logbook of any change of the content of PSMF/PSSF file made within the last five years except the changes in annexes and the following QPPV/LSR information: CV, contact details, back-up arrangements and contact person for pharmacovigilance on the national level. In addition, other change control documentation shall be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

2.2.5. Change control, logbook, versions and archiving

It is necessary for marketing authorization holders to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the pharmacovigilance system master file accordingly. EDA may solicit information about important changes to the pharmacovigilance system, such as, but not limited to:

- Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
- Organizational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of pharmacovigilance system master file management.

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

Changes to the pharmacovigilance system master file shall be recorded, such that a history of changes are available (specifying the date and the nature of the change), descriptive changes to the PSMF shall be recorded in a logbook.

Change history for the information contained in the Annexes may be on demand ‘, in which case the logbook would indicate the date of the revision of PSMF content and/or Annex update(s), the history of changes for Annex content would also be updated. Information that is being regularly updated and is contained in the Annexes, such as product and standard operating procedure lists or compliance figures, may include outputs from controlled systems (such as electronic document management systems or regulatory databases). The superseded versions of such content may be managed outside of the pharmacovigilance system master file content itself, provided that the history of changes is maintained and available to EDA on request. If the pharmacovigilance system master file has not been requested, or has remained unchanged for a period of time (for example, if the changes in the content of Annexes are managed outside of the pharmacovigilance system master file), it is recommended that a review is conducted periodically. Marketing authorizations holders need to ensure that the obligations concerning the timely provision of the pharmacovigilance system master file can be met. It is also noted that the QPPV shall be able to gain access to current and accurate information about the pharmacovigilance system, hence permanent access to the pharmacovigilance system master file shall be enabled, including the information contained in the Annexes (either via the pharmacovigilance master file itself or via access to the systems used to generate the Annex content).

Marketing authorization holders shall be able to justify their approach and have document control procedures in place to govern the maintenance of the pharmacovigilance system master file. As a basis for audit and inspections, the pharmacovigilance system master file provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

Changes to the pharmacovigilance system master file shall also account for shared pharmacovigilance systems and delegated activities. A record of the date and nature of notifications of the changes made available to EDA, the QPPV and relevant third parties shall be kept in order to ensure that change control is fully implemented.

The pharmacovigilance system master file shall be retained in a manner that ensures its legibility and accessibility.

As above mentioned, all Multinational MAHs/Applicants are required to submit the following two documents:

- **The PSMF** (it is accepted to be according to European Good Pharmacovigilance Practice which is the base for this guideline, All the regulations that will be described in this chapter apply to the PSMF of the multinational MAH/applicant), and
- **National pharmacovigilance sub-system file (national PSSF)** which describes the key elements of pharmacovigilance activities in Egypt, the national PSSF Pharmacovigilance sub-system file - shall include information and documents to describe the pharmacovigilance sub-system at the national level. The content of the national PSSF shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex. The national PSSF shall be maintained in a current state and be permanently available to the LSR.

The registration and continuous maintenance described in the registration and maintenance section is to be applied. The control associated with change of content as described in the relevant section is to be applied

The PSMF and PSSF shall be submitted with the same structure and within the same mentioned timelines for submission as clarified above and within this document, with consideration of the following:

The information that has be provided in each section shall focus on the national pharmacovigilance sub-system, and the description of the process, data handling and records for the performance of pharmacovigilance (on the national level and as appropriate in integration with MAH's headquarter).

2.2.6. Pharmacovigilance system master file presentation

The PSMF/PSSF shall be continuously accessible to the QPPV/LSR and to EDA on request. The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it shall be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements. Although provision of the document **within 14 days** of request by EDA is required, marketing authorization holders shall be aware that immediate access to the pharmacovigilance system master file may also be required by EDA, at the stated PSMF/PSSF location or QPPV/LSR site (if different).

*2.2.6.1.*Format and layout

The PSMF/PSSF file may be in electronic form on condition that a clearly arranged printed copy can be made available EDA if requested. In any format, the pharmacovigilance system master file shall be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the pharmacovigilance system master file in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF/PSSF in terms of change control and archiving.

The PSMF/PSSF shall be written in English (unless otherwise is requested by EDA), indexed in a manner consistent with the headings described in this Chapter, and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking

and searchable text is recommended. Documents such as copies of signed statements or agreements shall be included as appendices and described in the index.

The documents and particulars of PSMF/PSSF shall be presented with the following headings and, if hardcopy, in the order outlined:

Cover Page to include:

- The unique number assigned by EDA to the pharmacovigilance system master file (if applicable) shall also include, (company profile number, and commercial registry number).
- The name of the MAH, the MAH of the QPPV/LSR responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system)
- The list of pharmacovigilance system master files for the MAH (concerning products with a different pharmacovigilance system)
- The date of preparation / last update

The headings used in 2.2.4 shall be used for the main content of the pharmacovigilance system master file. The minimum required content of the Annexes is outlined in 2.2.4.8, and additional information may be included in the Annexes, provided that the requirements for the content of the main sections (2.2.1.7) are also met. The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

The Qualified Person responsible for pharmacovigilance /The LSR for national Pharmacovigilance sub-system, Annex A

- All documents for qualification and experience evidences. (Required for all PV staff).
- The list of tasks that have been delegated by the QPPV/LSR, or the applicable procedural document
- The curriculum vitae of the QPPV/LSR and associated documents
- Contact details

The Organizational Structure of the MAH, Annex B

- The lists of contracts and agreements
- Official organogram(s)
- A copy of the individual contractual agreements relevant to Egypt.

Sources of safety data, Annex C

Lists associated with the description of sources of safety data e.g. affiliates and third party

Contacts

Flow diagrams to indicate the main stages, timeframes and parties involved in safety data collection and its outcome

Computerized systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

Lists of procedural documents all applied procedures guidance e.g., Standard operating procedures (SOPs), work instructions (WIs)…etc.

Pharmacovigilance System Performance, Annex F

- Lists of performance indicators with evidence of used met
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules
- List of audits conducted and completed

Products, Annex H

- List(s) of products covered by the PSMF/PSSF
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself
- Documentation to support notifications and signatures concerning the PSMF/PSSF, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided shall still be named according to the format described. For example, Annex E shall **NOT** be renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used, Annex D shall simply be described as unused‘ in the indexing, in order that recipients of the pharmacovigilance system master file is assured that missing content is intended.

EDA may request any other additional documents which related to any PV activities or functions, and the MAH shall provide them in the related Annex as per the authority’s request.

2.3. Operation in Egypt

2.3.1. Responsibilities

2.3.1.1.Marketing authorization holders and applicants

Marketing authorization holders shall have a pharmacovigilance system in place to ensure the monitoring and supervision of one or more pharmaceutical products. They are also responsible for introducing and maintaining a pharmacovigilance system master file that records the pharmacovigilance system in place with regard to one or more authorized products. A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.

Applicants are required, at the time of initial marketing authorization application, to have in place a description of the pharmacovigilance system that records the system that will be in place and functioning at the time of grant of the marketing authorization and placing of the product on the market. During the evaluation of a marketing authorization application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review see 2.3.2.

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 EDA in the national pharmacovigilance systems list/database. The pharmacovigilance system master file shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these shall be clearly described as planned rather than established or current.

The pharmacovigilance system master file creation, maintenance in a current and accessible state (permanently available for audit and inspection purposes) and provision to EDA can be outsourced to a third party, but the marketing authorization holder retains ultimate responsibility for compliance with the legal requirements.

When the QPPV/LSR and related contact details change or when the location of the pharmacovigilance system master file changes, the marketing authorization holder is required to notify/submit the appropriate variation application(s) to EDA as applicable.

2.3.1.2.EDA

EDA is obliged to supervise the pharmacovigilance systems of marketing authorization holders. The full pharmacovigilance system master file may also be requested at any time, for example, to review the description of a pharmacovigilance system of an applicant that has not previously held a marketing authorization in Egypt or where specific concerns about the pharmacovigilance system and/or the product safety profile exist, and in preparation for an inspection (see Chapter 3). Information concerning changes to the summary information or content of the pharmacovigilance system master file will also be used to inform inspection planning and conduct.

In EDA, information about pharmacovigilance systems will be used to inform national risk-based pharmacovigilance inspection programs. Pharmacovigilance inspectors will report non-compliance with the requirements of legislation and guidance, including both non-compliance with the requirements for the pharmacovigilance system master file and the pharmacovigilance system (see Chapter 3).

EDA shall 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.

2.3.2. Accessibility/ submission of the pharmacovigilance system master file

The pharmacovigilance system master file shall be maintained in a current state and be permanently available to the QPPV. It shall also be permanently available for inspection, at the site where it is kept (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced.

The marketing authorization holder shall maintain and make available on request a copy of the pharmacovigilance system master file. The marketing authorization holder shall submit the copy within 14 days after receipt of the request from EDA (unless otherwise stated in the request). The pharmacovigilance system master file shall be submitted in a readable electronic format.

In the situation where the same pharmacovigilance system master file is used by more than one marketing authorization holder (where a common pharmacovigilance system is used) the concerned pharmacovigilance system master file shall be accessible to each, as any of the applicable marketing authorization holders shall be able to provide the file to EDA within 14 days, upon request (unless otherwise stated in the request).

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

- The applicant has not previously held a marketing authorization in Egypt, full PSMF is appropriate to review the description of a pharmacovigilance system;
- The applicant has not previously submitted the PSMF in Egypt or is in the process of establishing a new pharmacovigilance system;
- The applicant has major changes in its pharmacovigilance system or in its organization, such as mergers and acquisitions, where an acquisition action plan shall be provided with the PSMF (clarifying the roles and responsibility of each party during the acquisition period).
- The applicant has major or critical findings in the previous pharmacovigilance system assessment by EDA;
- The applicant has a history or culture of pharmacovigilance non-compliance; previous information (e.g. inspection history and non-compliance notifications or information from other authorities). In addition to the submission of the full PSMF, if the marketing authorization holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted (see chapter 3);
- Where specific concerns about the pharmacovigilance system and/or the product safety profile exist;
- Any other situation as seen appropriate by EDA;

Except in the above situations, the pharmacovigilance system master file shall not routinely be requested during the assessment of new marketing authorization applications (i.e. pre authorization), but may be requested on an **ad hoc basis**, particularly if a new pharmacovigilance system is being implemented, or if product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified or in preparation for a pharmacovigilance inspection.

The full PSMF (along together with its summary) may be requested to be submitted Post - authorization in the following situations:

Particularly if a new pharmacovigilance system is being implemented or

If product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified; or

In preparation for a pharmacovigilance inspection.

Any time upon request of EDA.

<u>For multinational MAHs/ applicants:</u>

The PSMF and the national PSSF shall be maintained in a current state and be permanently available to be submitted.

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 as described above concerning the applicability on global and local level. In case that these situations apply to the national PSSF but not the PSMF; then the multinational MAH can submit the "summary of PSMF" & the "national PSSF", and vice versa.

Except in the above situations, the PSMF and/or the national PSSF (as appropriate) shall not routinely be requested during the assessment of new marketing authorization applications (i.e. pre-authorization), instead the "summary of PSMF" and "summary of national PSSF" shall be submitted.

2.3.2.1.Special considerations for the multinational MAHs/applicant

2.3.2.2.The PSMF general consideration

The content of the PSMF is accepted to be according to European Good Pharmacovigilance Practice which is the base for this guideline. All the regulations described above in this chapter apply to the PSMF of the multinational MAH/applicant.

2.3.2.3.The information to be contained in the national PSSF

The national pharmacovigilance sub-system file (national PSSF) shall include information and documents to describe the pharmacovigilance sub-system at the national level in Egypt. The content of the national PSSF shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex. The national PSSF shall be maintained in a current state and be permanently available to the LSR.

The registration and continuous maintenance described in the 2.2.2. apply. The control associated with change of content as described in section 2.2.5. apply.

3. Pharmacovigilance Inspection

3.1. Introduction

This Chapter provides guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in Egypt, and outlines the role of the different parties involved. General guidance is provided under structures and processes section, while operation in Egypt section covers the overall operation of pharmacovigilance inspections in Egypt.

In order to determine that marketing authorization holders comply with pharmacovigilance obligations established within Egypt, and to facilitate compliance, EDA shall conduct pharmacovigilance inspections of marketing authorization holders or any firms employed to fulfil marketing authorization holder's pharmacovigilance obligations. Such inspections shall be carried out by inspectors appointed by EDA and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorization holder or any firms employed by the marketing authorization holder to perform the pharmacovigilance activities.

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 which may pose a risk to public health;
- To use the inspection results as a basis for enforcement action, where considered necessary

For marketing authorization holders of products in Egypt, it is the responsibility of EDA to verify, that the marketing authorization holder for the pharmaceutical product satisfies the national pharmacovigilance requirements. The pharmacovigilance system master file shall be located either where the main pharmacovigilance activities of the marketing authorization holder are performed or where the qualified person responsible for pharmacovigilance operates. EDA may conduct pre-authorization inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system.

Pharmacovigilance inspection programs will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate "for cause" inspections, which have been triggered to examine suspected non-compliance or potential risks, usually with impact on a specific product(s).

The results of an inspection will be provided to the inspected entity, who will be given the opportunity to comment on any non-compliance identified. Any non-compliance shall also be rectified by the marketing authorization holder in a timely manner through the implementation of a corrective and preventive action plan.

If the outcome of the inspection is that the marketing authorization holder does not comply with the pharmacovigilance obligations, EDA shall take the necessary measures to ensure that a marketing authorization holder is subject to effective, proportionate and dissuasive penalties.

Sharing of information and communication between pharmacovigilance inspectors and assessors is very important to ensure successful prioritization and targeting of these inspections and for the proper follow-up of inspections and the provision of recommendations on actions to be taken.

3.2. Structures and processes

3.2.1. Inspection types

3.2.1.1.System and product-related inspections

Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

3.2.1.2.Routine and "for cause" pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programs. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities shall be implemented. 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 Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

For cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For cause inspections 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. However, full system inspections may also be performed resulting from a trigger. For cause inspections may arise when, for example, one or more of the triggers listed below are identified:

- Risk-benefit balance of the product:
  - Change in the risk-benefit balance where further examination through an inspection is considered appropriate;
  - Delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
  - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to EDA, as applicable;
  - Non- compliance or product safety issues identified during the monitoring of pharmacovigilance activities by EDA;
  - Suspension or product withdrawal with no advance notice to EDA;
- Reporting obligations (expedited and periodic):
  - Delays or omissions in reporting;
  - Poor quality or incomplete reports;
  - Inconsistencies between reports and other information sources;
- Requests from EDA:
  - Failure to provide the requested information or data within the deadline specified by EDA;
  - Poor quality or inadequate provision of data to fulfil requests for information from EDA;

- Fulfilment of commitments:
  - Concerns about the status or fulfilment of risk management plan (RMP) commitments;
  - Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization;
  - Poor quality of reports requested as specific obligations;
- Inspections
  - Delays in the implementation or inappropriate implementation of corrective and preventive actions;
  - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);
  - Inspection information received from other international authorities, which may highlight issues of non-compliance;
- Others:
  - Concerns following review of the pharmacovigilance system master file;
  - Non- inspection related information received from other authorities, which may highlight issues of non-compliance;
  - Other sources of information or complaints.

3.2.1.3.Pre-authorization inspections

Pre-authorization pharmacovigilance inspections are inspections performed before a marketing authorization is granted. These inspections are conducted 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. Pre-authorization inspections are not mandatory, but may be requested in specific circumstances. Principles and procedures for requesting pre-authorization inspections shall be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorization. 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 in Egypt or is in the process of establishing a new 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. If the marketing authorization holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted;
- Due to product-specific safety concerns, it may be considered appropriate to examine the applicant ‘s ability:
  - To Implement product specific risk-minimisation activities; or
  - To Meet specific safety conditions which may be imposed; or
  - To manage routine pharmacovigilance for the product of concern (e.g. anticipated significant increase in adverse reaction reports when compared to previous products).

In most cases, a risk assessment based on a combination of product-specific and system-related issues shall 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 to confirm that critical findings and recommendations have been addressed;
- Granting of the marketing authorization with the recommendation to perform an early post-authorization pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the national routine program of pharmacovigilance inspections in Egypt (see 3.2.2.);
- Imposition of safety conditions to the marketing authorization.

3.2.1.4.Post-authorization inspections

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. They can be any of the types mentioned under 3.2.1.1 and 3.2.1.2.

3.2.1.5.Announced and unannounced inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

3.2.1.6.Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritize re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

3.2.1.7.Remote inspections

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorization holder or firms employed by the marketing authorization holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside Egypt or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an onsite inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the

inspection. The logistical aspects of the remote inspection shall be considered following liaison with the marketing authorization holder.

Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

3.2.2. Inspection planning

Pharmacovigilance inspection planning shall 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. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programs. Sharing of information and communication between pharmacovigilance inspectors and assessors is important to ensure successful prioritization and targeting of these inspections.

Factors which may be taken into consideration, as appropriate, by EDA when establishing pharmacovigilance inspection programs include, but are not limited to:

- Inspection related:
  - Compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP);
  - Re- inspection date recommended by the inspectors or assessors as a result of a previous inspection;
- 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) or designation for additional monitoring;
  - Product(s) with large sales volume, i.e. products associated with large patient exposure in Egypt;
  - Product(s) with limited alternative in the market place;
- Marketing authorization holder related:
  - Marketing authorization holder with many products on the market in Egypt.
  - Resources available to the marketing authorization holder for the pharmacovigilance activities they undertake;
  - Marketing authorization holder with no previous marketing authorizations in Egypt;
  - Negative information and/or safety concerns raised by EDA, other bodies/medicines authorities outside Egypt concerned or other areas (i.e. GCP, GMP, GLP and GDP);
  - Changes in the marketing authorization holder organization, such as mergers and acquisitions;
- Pharmacovigilance system related:
  - Marketing authorization holder with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance (QPPV) in Egypt, reporting of safety data etc.) and/or multiple firms employed to perform pharmacovigilance activities;
  - Change of QPPV/local safety responsible (LSR) since the last inspection;

- Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
- Delegation or transfer of pharmacovigilance system master file management.

EDA may solicit information from marketing authorization holders for risk-based inspection planning purposes if it is not readily available elsewhere.

3.2.3. Sites to be inspected

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorization holder may be inspected, in order to confirm their capability to support the marketing authorization holder ‘s compliance with pharmacovigilance obligations.

The sites to be inspected may be located in or outside Egypt. Inspections of sites outside Egypt might be appropriate where the main pharmacovigilance center, databases and/or activities are located outside Egypt and it would be otherwise inefficient or impossible to confirm compliance from a site within Egypt. EDA may cooperate in the coordination of inspections in other countries.

The type and number of sites to be inspected shall be selected appropriately to ensure that the key objectives within the scope of the inspection are met.

3.2.4. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by EDA and whether it is a system or product-related inspection (a description of the types of inspection, inspection triggers and points to consider for the different types of inspection is provided in 3.2.1).

The following elements shall be considered when preparing the scope of the inspection, as applicable:

- Information supplied in the pharmacovigilance system master file;
- Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from EDA such as the “National Pharmacovigilance and Safety reports database” reporting and data quality audits;
- Specific triggers (see 3.2.1.2. for examples of triggers);

It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

3.2.4.1.Routine pharmacovigilance inspections

Routine pharmacovigilance inspections shall examine compliance with EDA legislation and guidance, and the scope of such inspections shall include the following elements, as appropriate:

- Individual case safety reports (ICSRs):
  - Collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed

to fulfil marketing authorization holder ‘s pharmacovigilance obligations and departments other than drug safety;

- Assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of domestic ICSRs (from within Egypt), examples of ICSRs reported from outside Egypt shall be examined as part of this review (if applicable);
- Follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
- Reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
- Record keeping and archiving for ICSRs;

- Periodic safety update reports (PSURs);
  - Completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
  - Addressing safety topics, providing relevant analyses and actions;
  - Formatting according to requirements;
  - Timeliness of submissions;
- Ongoing safety evaluation;
  - Use of all relevant sources of information for signal detection;
  - Appropriately applied methodology concerning analysis;
  - Appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
  - Implementation of the RMP, or other commitments, e.g. conditions of marketing authorization;
  - Timely identification and provision of complete and accurate data to EDA, in particular in response to specific requests for data;
  - Implementation of approved changes to safety communications and product information, including internal distribution and external publication;
- Non-interventional clinical trials:
  - Reporting suspected unexpected serious adverse reactions (SUSARs) and non-interventional study cases according to the national regulations;
  - Receiving, recording and assessing cases from non-interventional trials (see ICSRs);
  - Submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorization efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
  - Appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
  - The inclusion of study data in ongoing safety evaluation;
- Pharmacovigilance system:
  - QPPV/ LSR roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
  - The roles and responsibilities of the marketing authorization holder in relation to the pharmacovigilance system;
  - accuracy, completeness and maintenance of the pharmacovigilance system master file;

- quality and adequacy of training, qualifications and experience of staff;
- coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- fitness for purpose of computerized systems;
- contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.
- As a general approach, a marketing authorization holder shall be inspected on the basis of risk-based considerations, but it is recommended to routinely inspect MAH at least once every 4 years.

The inspection may include the system for the fulfilment of conditions of a marketing authorization and the implementation of risk–minimization activities, as they relate to any of the above safety topics.

3.2.4.2.For cause inspections

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed in 3.2.4.1 and below, may be relevant:

- QPPV/LSR involvement and awareness of product-specific issues;
- In-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

3.2.4.3.Re-inspections

For the scope of a re-inspection, the following aspects shall be considered:

- Review of the status of the system and/or corrective and preventive action plan(s) resulting from previous pharmacovigilance inspection(s);
- Review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in QPPV/LSR as appropriate);
- Review of process and/or product-specific issues identified from the assessment of information provided by the marketing authorization holder, or not covered in a prior inspection.

The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example if a long time has elapsed since the previous inspection, in which case the elements listed in 3.2.4.1 may be considered for the inspection scope, as appropriate.

3.2.5. Inspection process

Pharmacovigilance inspections shall be planned, coordinated, conducted, reported on, followed-up and documented in accordance with national inspection procedures.

The pharmacovigilance inspections procedure will cover, at least, the following processes:

- Sharing of information;
- Inspection planning;
- Pre-authorization inspections;

- Coordination of third country inspections (including inspections of contractors in third countries);
- Preparation of pharmacovigilance inspections;
- Conduct of pharmacovigilance inspections;
- Reporting of pharmacovigilance inspections and inspection follow-up;
- Communication and prioritisation of pharmacovigilance inspections and findings;
- Interaction with national pharmacovigilance committee (if applicable) in relation to inspections and their follow-up;
- Record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
- Unannounced inspections;
- Sanctions and enforcement in case of serious non-compliance;
- Recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

These procedures will be revised and updated as deemed necessary. New procedures may also be developed when the need is identified in relation to the inspection process.

3.2.6. Inspection 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. The following follow-up actions shall be considered, as appropriate:

- Review of the marketing authorization holder ‘s corrective and preventive action plan;
- Review of the periodic progress reports, when deemed necessary;
- Re-inspection to assess appropriate implementation of the corrective and preventive action plan;
- Requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;
- Requests for issuing safety communications, including amendments of marketing and/or advertising information;
- Requests for a meeting with the marketing authorization holder to discuss the deficiencies, the impact of the deficiencies and action plans;
- Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorizations or clinical trial authorizations).

At EDA, sharing information and communication between pharmacovigilance inspectors and assessors is important for the proper follow-up of inspections and the provision of recommendations on actions to be taken.

3.2.7. Regulatory actions and sanctions

According to the national legislations and regulations, in order to protect public health, EDA is responsible to ensure compliance with pharmacovigilance obligations. In case of non-compliance with pharmacovigilance obligations, the necessary action will be taken on a case-by-case basis.

What action is taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. Moreover, service considerations may be imposed on the holders of marketing authorizations in case of violation of regulation as applicable. In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- Education and facilitation: EDA may communicate with marketing authorization holder representatives (e.g. in a meeting) to summarize the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorization holder ‘s proposals for corrective and preventive actions;
- Inspection: non-compliant marketing authorization holders may be 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; these are instruments which EDA may issue stating the legislation and guideline that has been breached, reminding marketing authorization holders of their pharmacovigilance obligations or specifying the steps that the marketing authorization holder shall take and in what timeframe order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- EDA may consider making public a list of marketing authorization holders found to be seriously or persistently non-compliant;
- Actions against a marketing authorization(s) or authorization application(s) e.g.
  - Urgent Safety Restriction;
  - Variation of the marketing authorization;
  - Suspension or revocation of the marketing authorization;
  - Delays in approvals of new marketing authorization applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorizations;
  - Requests for pre-authorization inspections;
- Product recalls e.g. where important safety warnings have been omitted from product information;
- Action relating to marketing or advertising information;
- Amendments or suspension of clinical trials due to product-specific safety issues;
- Administrative penalties, usually fixed fines or levied on a monthly interval;
- Referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

3.2.8. Record management and archiving

The principles and requirements to be followed will be described in the procedure on Record Keeping and Archiving of Documents Obtained or Resulting from the Pharmacovigilance Inspections referred to in 3.2.5

3.2.9. Qualification and training of inspectors

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by EDA shall be officials of, or appointed by, EDA in accordance with national regulation and follow the provisions of EDA.

It is recommended that inspectors are appointed based upon their experience (especially in pharmacovigilance) and the minimum requirements defined by EDA. In addition, consideration shall be given to the recommendations for training and experience described in the pharmacovigilance inspections procedures.

The inspectors shall undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections. They shall also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes shall be in place in order to ensure that inspection competencies are maintained. In particular, inspectors shall be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience shall be documented individually and evaluated according to the requirements of the applicable quality system of EDA.

3.2.10. Quality management of pharmacovigilance inspection process

Quality of the pharmacovigilance inspection process is managed by EDA and covered by their pharmacovigilance systems and associated quality systems, meaning that the process is also subject to audit. Guidance on establishment and maintenance of a quality assured pharmacovigilance system is provided in chapter 1.

3.3. Operation in Egypt

This section describes the operation of pharmacovigilance inspections in Egypt, it defines the roles and the responsibilities of PV stakeholders concerned with this guideline.

3.3.1. Role of EDA

EDA shall establish the legal and administrative framework within which pharmacovigilance inspections operate, including the definition of the rights of inspectors for inspecting pharmacovigilance sites and access to pharmacovigilance data.

EDA shall provide sufficient resources and appoint adequately qualified inspectors to ensure effective determination of compliance with good pharmacovigilance practice (GVP). The inspector(s) appointed may be accompanied, when needed, by expert(s) on relevant areas.

Pharmacovigilance inspections shall be planned, coordinated, conducted, reported on, followed-up and documented in accordance with national inspection procedures. The scheduling and conduct of these inspections will be driven by the preparation of inspection programs based on a systematic and risk-based approach as outlined in 3.2.2.

3.3.2. Inspection Programs

A program for routine inspections for authorized products in Egypt will be determined by EDA. These inspections will be prioritized based on the potential risk to public health, considering the factors listed in 3.2.5. As a general approach, a marketing authorization holder shall be inspected on the basis of risk-based considerations, but it is recommended to routinely inspect MAH at least once every 4 years.

If the same pharmacovigilance system is used for a variety of authorizations, then the results of EDA inspection may be applicable for all products covered by that system.

This routine inspection programme will be separate from any “for cause” inspections, but if a “for cause” inspection takes place it may replace the need for one under this programme, dependent on its scope.

EDA is also responsible for the planning and coordination of pharmacovigilance inspections in order to ensure compliance with the national legislation and to verify the effectiveness of the marketing authorization holder ‘s pharmacovigilance system.

Based on the information from other inspections, EDA will prioritize the inspections in its programme and will use the information for the preparation of an appropriate scope for the inspection. For example, EDA may seek to verify the fulfilment of requirements concerning the implementation of specific risk-minimization measures, communications concerning safety, locally conducted safety studies, or issues linked to national health care systems. A broader examination of pharmacovigilance applied to particular products of national interest may also be appropriate.

Deficiencies are classified by the assessed risk level and may vary depending on the nature of medicine. In some circumstances an otherwise major deficiency may be categorized as critical.

A deficiency reported after a previous inspection and not corrected may be given higher classification.

3.3.3. Role of the Marketing Authorization Holders and Applicants

Marketing authorization holders with authorized products and applicants who have submitted new applications subject to pharmacovigilance inspections (see 3.2.1). Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

- Always to be inspection-ready as inspections may be unannounced.
- To maintain and make available to the inspectors on request, no later than 14 days after the receipt of a request, the pharmacovigilance system master file.
- To ensure that the sites selected for inspection, which may include firms employed by the marketing authorization holder (third party) to perform pharmacovigilance activities, agree to be inspected before the inspection is performed.
- To make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection.
- To ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified.
- To ensure that relevant pharmacovigilance data is accessible
- To ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritization of critical and/or major findings.

4. Pharmacovigilance Audits

4.1. Introduction

For the purposes of this chapter reference to pharmacovigilance audit(s) and pharmacovigilance audit activity(ies) are deemed to include pharmacovigilance system audits and audit(s) of the quality system for pharmacovigilance activities.

The overall description and objectives of pharmacovigilance systems and quality systems for pharmacovigilance activities are referred to in chapter 1, while the specific pharmacovigilance processes are described in each respective chapter of GVP.

This chapter provides guidance on planning and conducting the legally required audits, the role, context and management of pharmacovigilance audit activity. This chapter is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonization, and encourage consistency and simplification of the audit process. The principles in this chapter are aligned with internationally accepted auditing standards, issued by relevant international auditing standardization organizations[2] and support a risk-based approach to pharmacovigilance audits.

Section 4.2 outlines the general structures and processes that shall be followed to identify the most appropriate pharmacovigilance audit engagements and describes the steps which can be undertaken by marketing authorization holders to plan, conduct and report upon an individual pharmacovigilance audit engagement. This Section also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

Section 4.3 provides an outline of the operation in Egypt in respect of pharmacovigilance audits.

Note: For different definitions, refer to the definition annex of this guidance

4.2. Structures and processes

The structures and the processes of pharmacovigilance audits in Egypt has to be implemented following the Good Pharmacovigilance practice (GVP). This topic explains multiple items that shall be considered in implementation such as: PV audit and its objectives, the risk-based approach to PV audits, and quality system and record management practices.

4.2.1. Pharmacovigilance audit and its objective

Pharmacovigilance audit activities shall verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.

In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are, for each audit objective, the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria shall reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation and guidance.

Note:

Benchmarking, reviews of qualifications, risk assessment questionnaires, surveys or other activities in which evidence of fulfilment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit.

4.2.2. The risk-based approach to pharmacovigilance audits

A risk-based approach 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 and/or likelihood of non-detection by other methods. The risk-based approach to audits focuses on the areas of highest risk to the organization's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- Strategic level audit planning resulting in an audit strategy (long term approach), which shall 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; and
- Operational level audit planning resulting in an audit plan for individual audit engagements, prioritizing audit tasks based on risk and utilizing 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 (see 4.2.2.3)

Risk assessment shall be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organization (see 4.2.2.1., 4.2.2.2. and 4.2.2.3. respectively).

4.2.2.1.Strategic level audit planning

The audit strategy is a high level statement of 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 includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

The audit strategy shall cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:

- All pharmacovigilance processes and tasks;
- The quality system for pharmacovigilance activities;
- Interactions and interfaces with other departments, as appropriate;
- Pharmacovigilance activities conducted by affiliated organizations or activities delegated to another organization (e.g. regional reporting centers, MAH affiliates or third parties, such as contract organizations and other vendors).

This is a non-prioritized, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment:

- Changes to legislation and guidance;

- Major re-organization or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorization holders, this may lead to a significant increase in the number of products for which the system is used);
- Change in key managerial function(s);
- Risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organization, increase in volumes of work;
- Significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;
- First pharmaceutical product on the market (for a marketing authorization holder);
- Pharmaceutical product(s) on the market with specific risk minimization measures or other specific safety conditions such as requirements for additional monitoring;
- Criticality of the process, e.g.:
  - For EDA: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
  - For marketing authorization holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorization holder shall consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorization holder, in addition to considering the other factors included in this list;
- Outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritized depending on criticality); if the area/process has previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;
- Identified procedural gaps relating to specific areas/processes;
- Other information relating to compliance with legislation and guidance, for example:
  - For EDA: information from compliance metrics from complaints, from external sources, e.g. audits/assessments of the EAD that may be conducted by external bodies;
  - For marketing authorization holders: information from compliance metrics from inspections (see chapter 3), from complaints, from other external sources, e.g. audits;
- Other organizational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

4.2.2.2.Tactical level audit planning

An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It shall be prepared in line with the long term audit strategy. The audit programme shall be approved by upper management with overall responsibility for operational and governance structure.

The risk-based audit programme shall be based on an appropriate risk assessment and shall focus on:

- The quality system for pharmacovigilance activities;
- Critical pharmacovigilance processes (see for example chapter 1);
- Key control systems relied on for pharmacovigilance activities;
- Areas identified as high risk, after controls have been put in place or mitigating action taken.

The risk-based audit programme shall also take into account historical areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

The audit programme documentation shall include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.

The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme shall be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) shall be performed at regular intervals, which are in line with national legislative requirements.

Changes to the audit program may happen and will require proper documentation.

4.2.2.3.Operational level audit planning and reporting

Planning and fieldwork

The organization shall ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit shall be settled in the relevant audit related procedures, and the organization shall ensure that audits are conducted in accordance with the written procedures, in line with this guideline.

Individual pharmacovigilance audits shall be undertaken in line with the approved risk-based audit programme (see 4.2.2.2). When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate risk based sampling and testing methods, documenting the audit approach in an audit plan.

Reporting

The findings of the auditors shall be documented in an audit report and shall be communicated to management in a timely manner. The audit process shall include mechanisms for communicating the audit findings to the auditee and receiving feedback, and reporting the audit findings to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings shall be reported in line with their relative risk level and shall be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system shall be defined in the description of the quality system for pharmacovigilance, and shall take into consideration the thresholds noted below which would be used in further reporting under the legislation as set out in section 4.3.2:

- **Critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements. It may include a

pattern of deviations classified as major. It also includes the engaging in fraud, misrepresentation or falsification of data.

- **Major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious. It may include a pattern of deviations classified as minor.
- **Minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients. A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Issues that need to be urgently addressed shall be communicated in an expedited manner to the auditee‘s management and the upper management.

4.2.2.4.Actions based on audit outcomes and follow-up of audits

Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. Corrective and preventive actions to address critical and major issues shall be prioritized. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on nature of findings and the planned action(s).

The management of the organization is responsible for ensuring that the organization has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions shall include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.

Upper management and those charged with governance, shall ensure that effective action is implemented to address the audit findings. The implementation of agreed actions shall be monitored in a systematic way, and the progress of implementation shall be communicated on a periodic basis proportionate to the planned actions to upper management.

Evidence of completion of actions shall be recorded in order to document that issues raised during the audit have been addressed.

Capacity for follow-up audits shall be foreseen in the audit programme. They shall be carried out as deemed necessary, in order to verify the completion of agreed actions.

4.2.3. Quality system and record management practices

4.2.3.1. Competence of auditors and quality management of audit activities

Independence and objectivity of audit work and auditors

The organization shall assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities shall be independent. The organization’s

management shall ensure this independence and objectivity in a structured manner and document this.

Auditors shall be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results. The main reporting line shall be to the upper management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion. Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however, auditors shall maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires auditors not to subordinate their judgement on audit matters to that of others.

Qualifications, skills and experience of auditors and continuing professional development

Auditors shall demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, shall cover knowledge, skills and abilities in:

- Audit principles, procedures and techniques;
- Applicable laws, regulations and other requirements relevant to pharmacovigilance;
- Pharmacovigilance activities, processes and system(s);
- Management system(s);
- Organizational system(s).

Evaluation of the quality of audit activities

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, auditee feedback and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance to code of conduct, audit programme, and audit procedures).

Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization (i.e. within EDA or marketing authorization holder). The organization may require the use of an outsourced audit service provider, this is accepted but does not replace the importance of the presence of an internal department responsible for quality and compliance monitoring. Where the organization decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP chapter and perform pharmacovigilance audits:

- The requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements shall be specified to the outsourced service providers, by the organization, in writing;
- The scope, objectives and procedural requirements for the audit shall be specified to the outsourced service provider, by the organization, in writing;
- The organization shall obtain and document assurance of the independence and objectivity of outsourced service providers;
- The outsourced audit service provider shall also follow the relevant parts of this GVP chapter.

Retention of audit reports

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in chapter 1.

4.3. Operation in Egypt: Pharmacovigilance audit policy framework and organizational structure

4.3.1. Requirement to perform an audit for Marketing authorization holders in Egypt

The marketing authorization holder in Egypt is required to perform regular risk-based audit(s) of their pharmacovigilance system, including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements. The dates and results of audits and follow-up audits shall be documented.

See 4.3.2. for further details of the requirements for audit reporting by the marketing authorization holder.

4.3.1.1.The qualified person responsible for pharmacovigilance (QPPV)/LSR

The responsibilities of the QPPV in respect of audit are provided in chapter 1. Furthermore, the QPPV shall receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions.

The QPPV shall be notified of any audit findings relevant to the pharmacovigilance system irrespective of where the audit was conducted.

For multinational MAH; the local safety responsible (LSR) in Egypt where the audit to be conducted shall receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions on national level.

Furthermore, the concerned LSR shall be notified of any audit findings relevant to the pharmacovigilance system in Egypt.

4.3.2. Requirements for audit reporting by the marketing authorization holder in Egypt

The marketing authorization holder shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF) (see chapter 2). Based on the audit findings, the marketing authorization holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file (see chapter 2).

The marketing authorization holders shall ensure that a list of all scheduled and completed audits is kept in the annex to the pharmacovigilance system master file and that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies. The dates and results of audits and follow-up audits shall be documented.

4.3.3. Confidentiality

Documents and information collected by the internal auditor shall be treated with appropriate confidentiality and discretion, and also respect national legislation on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

5. Risk Management systems

5.1. Introduction

A pharmaceutical product is authorized on the basis that in the specified indication(s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Generally, a pharmaceutical product will be associated with adverse reactions and these will vary in terms of severity, likelihood of occurrence, effect on individual patients and public health impact. However, not all adverse reactions and risks will have been identified at the time when an initial marketing authorization is granted and some will only be discovered and characterized in the post-authorization phase.

The aim of a risk management plan (RMP) is to document the risk management system considered necessary to identify, characterize and minimize a pharmaceutical product's important risks. To this end, the RMP contains:

- The identification or characterization of the safety profile of the pharmaceutical product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the safety specification).
- The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions (the pharmacovigilance plan).
- The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the risk minimization plan).

As knowledge regarding a pharmaceutical product's safety profile increases over time, so will the risk management plan change.

Marketing authorization applicants are encouraged to plan from very early on in a product's life cycle how they will further characterize and minimize the risks associated with the product in the post-authorization phase.

This Chapter includes the principles of risk minimization and shall be read in conjunction with GVP Chapter "Risk minimization measures: selection of tools and effectiveness indicators"

5.1.1. Terminology

5.1.1.1.Identified risk

An untoward occurrence for which there is *adequate evidence of an association with the pharmaceutical product* of interest. Examples include:

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure.

5.1.1.2.Potential risk

An untoward occurrence for which there is **some basis for suspicion of an association with the pharmaceutical product** of interest but where this association has not been confirmed. Examples include:

- Toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;
- Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship;
- A signal arising from a spontaneous adverse reaction reporting system;
- An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the pharmaceutical product.

5.1.1.3.Missing information

Gaps in knowledge about a pharmaceutical product, related to safety or use in particular patient populations, which could be clinically significant.
Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

5.1.1.4.Important identified risk and important potential risk

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.What constitutes an **important** risk will depend upon several factors, including the *impact on the individual, the seriousness of the risk, and the impact on public health*. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information shall be considered important.

Notes:

- The RMP shall focus on the **important identified risks** that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant:
    - Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk)
    - Risk minimization activities: product information advising on specific clinical actions to be taken to minimize the risk, or additional risk minimization activities.
- The **important potential risks** to be included in the RMP are those important potential risks that, when further characterized and if confirmed, would have an impact on the risk-benefit balance of the pharmaceutical product. Where there is a scientific rationale that an

adverse clinical outcome might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product, the adverse reaction shall be considered a potential risk, and if deemed important, shall be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

- **Missing information** relevant to the risk management planning refers to gaps in knowledge about the safety of a pharmaceutical product for certain anticipated utilization (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning shall focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

5.1.1.5.Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to pharmaceutical products including the assessment of the effectiveness of those activities and interventions.

5.1.1.6.Risk management plan

A detailed description of the risk management system.

5.1.1.7.Risk minimization activity (used synonymously with risk minimization measure)

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

5.1.1.8.Safety concern

An important identified risk, important potential risk or missing information.

5.2. Structures and processes

5.2.1. Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular pharmaceutical product exceed the risks by the greatest achievable margin. The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a pharmaceutical product's life cycle. The risk management system shall be proportionate to the identified risks and the potential risks of the pharmaceutical product, and the need for post-authorization safety data.

The RMP is a dynamic document that shall be updated throughout the life cycle of the product(s). This includes the addition of safety concerns where required, but also, as the safety profile is further characterized, the removal or reclassification of safety concerns.

The guidance on risk classification in this document may facilitate that during the life cycle of the products the list of safety concerns in the RMP will be reduced:

- It may be that important potential risks can be removed from the safety specification in the RMP (e.g. when accumulating scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important, or when there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk), or they need to be reclassified to important identified risks (e.g. if scientific and clinical data strengthen the association between the risk and the product).

- In certain circumstances, where the risk is fully characterized and appropriately managed, important identified risks may be removed from the safety specification (e.g. for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimization activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines).

- Given the overall aim of obtaining more information regarding the risk-benefit balance in certain populations excluded in the pre-authorization phase, it is expected that as the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information.

The need to continue additional risk minimization activities may change, as the recommendations for specific clinical measures to address the risk become part of the routine practice such as inclusion into standard treatment protocols in Egypt, or in response to the findings of effectiveness of risk minimization evaluations (i.e. they may need to be replaced with more effective activities). Some risk minimization activities might be needed to be retained for the lifetime of the pharmaceutical product (e.g. pregnancy prevention programs).

5.2.2. Responsibilities for risk management

The principal organizations directly involved in pharmaceutical products' risk management planning are applicants /marketing authorization holders and EDA who regulate the pharmaceutical products.

5.2.2.1.Marketing authorization holders and applicants

In relation to risk management of its pharmaceutical products, an applicant/marketing authorization holder is responsible for:

- ensuring that it constantly monitors the risks of its pharmaceutical products in compliance with relevant legislation and reports the results of this, as required, to EDA.
- taking all appropriate actions to minimize the risks of the pharmaceutical product and maximize the benefits including ensuring the accuracy of all information produced by the company in relation to its pharmaceutical products, and actively updating and promptly communicating it when new information becomes available

Producing a RMP requires the input of different specialists and departments within and/or outside an organization. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts

depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimization activities shall involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it shall be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure.

Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorization applicant/holder who shall ensure oversight by someone with the appropriate scientific background within the company.

5.2.2.2.EDA

In relation to risk management, the principal responsibilities of EDA are constantly monitoring the benefits and risks of pharmaceutical products including assessing the reports submitted by pharmaceutical companies, healthcare professionals, patients and, where appropriate, other sources of information and taking appropriate regulatory actions to minimize the risks of the pharmaceutical

product including ensuring the accuracy and completeness of all information produced by the company in relation to its pharmaceutical products and ensuring the implementation of risk minimization activities in Egypt and effectively communicating with stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, healthcare physicians when necessary, ensuring that marketing authorization holders of generic and/or similar biological pharmaceutical products make similar changes to their risk minimization measures when changes are made to those of reference pharmaceutical product.

5.2.3. Objectives of a risk management plan

The RMP shall contain the following elements which:

- Identify or characterize the safety profile of the pharmaceutical product(s) concerned;
- Indicate how to characterize further the safety profile of the pharmaceutical product(s) concerned;
- Document measures to prevent or minimize the risks associated with the pharmaceutical product including an assessment of the effectiveness of those interventions;
- Document post-authorization obligations that have been imposed as a condition of the marketing authorization.

There is an implicit requirement that to fulfil these obligations a RMP shall also:

- Describe what is known and not known about the safety profile of the concerned pharmaceutical product(s);
- Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorization phase (also known as effectiveness studies);
- Include a description of how the effectiveness of risk minimization measures will be assessed.

5.2.4. Overview of the format and content of the risk management plan (RMP)

The RMP consists of seven parts. The submitted RMP shall follow the RMP template integrated / abridged formats [For RMP templates, refer to annex III.2 &III.3]. Part II of the RMP - Safety specification is subdivided into modules, so the content can be tailored to the specifics of the pharmaceutical product. RMP part II modules generally follow the section titles in the safety specification of ICH-E2E. The modular structure aims to facilitate the update of the RMP; in addition, in specific circumstances certain RMP sections may have reduced content requirements. However, the RMP document is expected to be submitted as one single document including all sections and annexes, as relevant.

Overview of the RMP parts and modules

Part I Product(s) overview

Part II Safety specification

Module SI Epidemiology of the indication(s) and target population(s)

Module SII Non-clinical part of the safety specification

Module SIII Clinical trial exposure

Module SIV Populations not studied in clinical trials

Module SV Post-authorization experience

Module SVI Additional requirements for the safety specification

Module SVII Identified and potential risks

Module SVIII Summary of the safety concerns

Part III Pharmacovigilance plan (including post-authorization safety studies)

Part IV Plans for post-authorization efficacy studies

Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Part VI Summary of the risk management plan

Part VII Annexes

5.2.5. Detailed description of each part of the risk management plan

The description of the parts and modules of an RMP provide guidance on the main topics which shall be covered within each specific area. However, some sections may not be relevant to all pharmaceutical products and there may be additional topics which need to be included but are not mentioned. The RMP is part of the scientific dossier of a product and as such shall be scientifically based and not be promotional.

5.2.6. RMP part I "Product(s) overview"

This shall provide the administrative information on the RMP and an overview of the product(s). The information presented shall be current and accurate in relation to the ongoing application as it is anticipated to appear in the marketing authorization. The information shall include:

5.2.6.1.Active substance information:

- Active substance(s);
- Pharmacotherapeutic group(s) (ATC code);
- Name of the marketing authorization holder or applicant
- Date and country of first authorization worldwide (if applicable);
- Date and country of first launch worldwide (if applicable);
- Number of pharmaceutical product(s) to which this RMP refers.

5.2.6.2.Administrative information on the RMP:

- Data lock point of the current RMP;
- Date submitted and the version number;
- List of all parts and modules of the RMP with date and version of the RMP when the part/modules was last updated and the RMP was last submitted.

5.2.6.3.Brief description of the product including:

- Chemical class;
- Summary of mode of action;
- Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- Indications: approved and proposed
- Dosage
- Pharmaceutical forms and strengths;
- Whether the product is subject to additional monitoring (at initial marketing authorization application conclusion or with RMP updates).

5.2.7. RMP part II "Safety specification"

The purpose of the safety specification is to provide an adequate discussion on the safety profile of the pharmaceutical product(s), with focus on those aspects that need further risk management activities. It shall include a summary of the important identified risks of a pharmaceutical product, important potential risks, and missing information. It shall also address the populations potentially at risk (where the product is likely to be used i.e. both as authorized and off-label use), and any outstanding safety questions that warrant further investigation to refine the understanding of the risk-benefit balance during the post-authorization period. The safety specification forms the basis of the pharmacovigilance plan and the risk minimization plan.

The safety specification consists of eight RMP modules, of which RMP modules SI-SV, SVII and SVIII correspond to safety specification headings in ICH-E2E.

5.2.7.1.RMP part II, module SI "Epidemiology of the indication(s) and target population(s)"

This RMP module shall include incidence, prevalence, outcome of the (untreated) target disease (i.e. indications) and relevant co-morbidity, and shall when relevant for assessment of safety and risk management be stratified by age, gender, and ethnic origin. Risk factors for the disease and the main existing treatment options shall also be described. The emphasis shall be on the epidemiology of the proposed indication. Differences in the epidemiology in different regions shall be discussed (where epidemiology varies across regions).

This section shall also describe the relevant adverse events to be anticipated in the (untreated) target population, their frequency and characteristics. The text shall help anticipate and interpret any potential signals and help identify opportunities for risk minimization. The text shall be kept concise and shall not include any element of a promotional nature.

5.2.7.2.RMP part II, module SII "Non-clinical part of the safety specification"

This RMP module shall present a high-level summary of the significant non-clinical safety findings, for example:

- Toxicity (key issues identified from acute or repeat-dose toxicity, reproductive/developmental toxicity, genotoxicity, carcinogenicity);
- Safety pharmacology (e.g. cardiovascular system, including QT interval prolongation, nervous system);
- Other toxicity-related information or data.

What constitutes an important non-clinical safety finding will depend upon the pharmaceutical product, the target population and experience with other similar compounds or therapies in the same class. Normally, significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans shall be discussed. Also, quality aspects if relevant to safety (e.g. genotoxic impurities) shall be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity shall be explicitly mentioned and the implications for use in this population discussed. Where the non-clinical safety finding could constitute an important potential risk to the target population, it shall be included as a safety concern in RMP module SVIII. Where the non-clinical safety finding is not considered relevant for human beings, provision of a brief explanation is required, but the safety finding is not expected to be carried forward to SVII and SVIII as a safety concern.

The content of this section shall be assessed for relevance over time. Post-authorization, this section would only be expected to be updated when new non-clinical data impact the list of safety concerns. Safety concerns identified on the basis of non-clinical data which are no longer relevant and/or have not been confirmed when sufficient relevant post-marketing experience and evidence are gathered, can be removed from the list of safety concerns.

5.2.7.3.RMP part II, module SIII "Clinical trial exposure"

In this RMP module, in order to assess the limitations of the human safety database, summary information on the patients studied in clinical trials shall be provided in an appropriate format (e.g. tables/graphs) at time of submission of the initial RMP or when there is a major update due to new exposure data from clinical studies (e.g. in a new indication). The content of this section shall be assessed for relevance over time and, in the absence of new significant clinical trial exposure data, this section does not need to be updated.

The size of the study population shall be detailed using both numbers of patients and, where appropriate, patient time exposed to the pharmaceutical product. This shall be stratified for relevant categories; stratifications would normally include:

- Age and gender;
- Indication;
- Dose;
- Other stratifications shall be provided where this adds meaningful information for risk management planning purposes.

When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route of administration, the clinical trial data specific to the application shall be presented separately at the start of the module as well as being pooled across all indications.

5.2.7.4.RMP part II, module SIV "Populations not studied in clinical trials"

Populations that are considered under missing information shall be described in this RMP module.

Information on the low exposure of special populations or the lack thereof (e.g. pregnant women, breast-feeding women, patients with renal impairment, hepatic impairment or cardiac impairment, populations with relevant genetic polymorphisms, immuno-compromised patients and populations of different ethnic origins) shall be provided where available and as appropriate. The degree of renal, hepatic or cardiac impairment shall be specified as well as the type of genetic polymorphism, as available.

If the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this shall be included as missing information in the RMP. Excluded populations from the clinical trial development programme shall be included as missing information only when they are relevant for the approved and proposed indications, i.e. "on-label", and if the use in such populations might be associated with risks of clinical significance. In discussing differences between target populations and those exposed in clinical trials it shall be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria. When such populations are proposed as missing information, then RMP module SIV shall also include a discussion on the relevant subpopulations.

If there is evidence that use in excluded populations is associated with an undesirable clinical outcome, then the outcome shall be included as an important (potential) risk.

5.2.7.5.RMP part II, module SV "Post-authorization experience"

If post-marketing data are available from post-authorization experience outside Egypt, where the product is already authorized or from other authorized products containing the same active substance, from the same marketing authorization holder, the data shall be discussed in this RMP module.

It shall only provide an overview of experience in the post-authorization phase that is helpful for risk management planning purposes. It is not the intention to duplicate information from the PBRER. Additionally, a discussion on how the pharmaceutical product is being used in practice

and on-label and off label use, including use in the special populations mentioned in RMP module SIV, can also be included when relevant for the risk identification discussion in module SVII.

5.2.7.6.RMP part II, module SVI "Additional requirements for the safety specification"

In addition to safety topics required, the following shall be addressed in the RMP: the potential for misuse for illegal purposes, and, where appropriate, the proposed risk minimization measures, e.g. limited pack size, controlled access programme, special medical prescription

5.2.7.7.RMP part II, module SVII "Identified and potential risks"

This RMP module shall provide a focused discussion on the identification of important identified and important potential risks, and missing information (i.e. safety concerns).

The following safety topics derived from specific situations/data sources are thought to be of particular interest for the risk identification discussion in module SVII, and shall be discussed when they lead to risks of the product:

- potential harm from overdose, whether intentional or accidental, for example in cases where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this shall be explicitly mentioned and, where relevant, the important risks following overdose shall be included as safety concerns in RMP module SVIII and appropriate risk minimization proposed in RMP part V;

- potential for risks resulting from medication errors, defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Medication errors leading to important risks, identified during product development including clinical trials, shall be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication shall be given of how these have been taken into account in the final product design.

- potential for transmission of infectious agents due to the nature of the manufacturing process or the materials involved. For live attenuated vaccines any potential for transmission of mutated live vaccine virus, and the potential of causing the disease in immunocompromised contacts of the vaccine shall be discussed with the view of considering them as important potential risks;

- potential for off-label use, when differences in safety concerns between the target and the off-label population are anticipated, the potential risks arising from the off-label use of the product shall be considered for inclusion in the safety specifications;

- if an important identified or potential risk common to other members of the pharmacological class is not thought to be an important identified or important potential risk with the concerned pharmaceutical product, the evidence to support this shall be provided and discussed; important risks related to identified and potential pharmacokinetic and pharmacodynamic interactions shall be discussed in relation to the treatments for the condition, but also in relation to commonly used medications in the target population. The evidence supporting the interaction and possible mechanism shall be summarized, the

potential health risks discussed for different indications and populations, and plans to further characterize and minimize the risks described. Important risks derived from interactions shall be included as a safety concern;

- risks in pregnant and lactating women, e.g. teratogenic risk - direct or through exposure to semen: contraception recommendations can be considered as risk minimization measures.
- effect on fertility - appropriate risk minimization measures shall be considered, e.g. routine risk communication and/or additional activities recommending fertility preservation: sperm cryopreservation in men and embryo and oocyte cryopreservation in women;
- risks associated with the disposal of the used product (e.g. transdermal patches with remaining active substance or remains of radioactive diagnostics).
- risks related to the administration procedure (e.g. risks related to the use of a medical device (malfunction which impacts on the dose administered, risk of variability in complex administrations);
- paediatric safety issues that are particular causes of concern in pediatric population, Potential long-term safety/efficacy issues in relation to pediatric use for consideration in the RMP/Pharmacovigilance activities.

5.2.7.8.RMP part II, module SVIII "Summary of the safety concerns"

In this RMP module, a list of safety concerns shall be provided with the following categories:

- Important identified risks;
- Important potential risks;
- Missing information.

5.2.8. RMP part III "Pharmacovigilance plan (including post-authorization safety studies)"

The purpose of the pharmacovigilance plan in part III of the RMP is to present an overview and discuss how the applicant/marketing authorization holder plans to further characterize the safety concerns in the safety specification. It provides a structured plan for:

- the investigation of whether a potential risk is confirmed as an identified risk or refuted;
- further characterization of safety concerns including severity, frequency, and risk factors;
- how missing information will be sought;
- measuring the effectiveness of risk minimization measures.

It does not include actions intended to reduce, prevent or mitigate risks; these are discussed in RMP part V.

The pharmacovigilance plan shall focus on the safety concerns summarized in RMP module SVIII of the safety specifications and shall be proportionate to the benefits and risks of the product. Early discussions between EDA and the applicant/marketing authorization holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed and consequently milestones shall be agreed.

Pharmacovigilance activities can be divided into routine and additional pharmacovigilance activities.

5.2.8.1.RMP part III section "Routine pharmacovigilance activities "

Routine pharmacovigilance is the primary/minimum set of activities required for all pharmaceutical products and shall be implemented for all safety concerns, it includes for example but not restricted to preparation of PBRER, Adverse events reporting, continuous monitoring & evaluation of the efficacy and safety profile, literature search and Signal detection, which is part of routine pharmacovigilance, is an important element in identifying new risks for all products.

Specific adverse reaction follow-up questionnaires

Where an applicant/marketing authorization holder is requested, or plans, to use specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest.

The follow up questionnaires are necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of such risks and shall address -but not restricted to- the following points:

- Patient demographics
- Details of Drug Therapy & indication for treatment
- Duration of therapy (including start dates) & dosage
- Details of Adverse Event
- Details of other concomitant drugs
- Details of any current risk factors for event (Please add specific questions addressing the risk related (relevant) risk factors (For example -but not restricted to-: alcohol use, exposure to contrast media, any hereditary diseases, infection/sepsis, renal disease, cardiac disorders)
- Laboratory Values / Tests Please add a statement asking the reporter to provide copies of risk related (relevant) laboratory tests printouts (For example -but not restricted to: serum, glucose, cardiac enzymes, kidney function, liver function, CBC, TSH)
- Details of medical history
- Details of Diagnostic Procedures Please add specific questions addressing the risk related Diagnostic Procedures & Please insert a statement asking the reporter to attach the reports clarifying the date of such procedures (For example -but not restricted to-: ECG, ECHO, X-ray, CT scan, MRI)
- Reporter Details

Other forms of routine pharmacovigilance activities

The description of the planned other forms of routine pharmacovigilance activities shall be described in the related section, e.g. the high level description of the enhanced passive surveillance system, observed versus expected analyses, cumulative reviews of adverse events of interest.

5.2.8.2.RMP part III section "Additional pharmacovigilance activities"

The applicant/marketing authorization holder shall list in this RMP section their planned additional pharmacovigilance activities, detailing what information is expected to be collected that can lead to a more informed consideration of the risk-benefit balance.

Additional pharmacovigilance activities are pharmacovigilance activities that are not considered routine. They may be non-clinical studies, clinical trials or non-interventional studies. Examples include long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterization of the long-term safety of the pharmaceutical product. When any doubt exists about the need for additional pharmacovigilance activities, consultation with EDA shall be considered.

Studies in the pharmacovigilance plan aim to identify and characterize risks, to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimization

activities.
They shall relate to the safety concerns identified in the safety specification, be feasible and shall not include any element of a promotional nature.

5.2.9. RMP part IV "Plans for post-authorization efficacy studies"

This RMP part shall include a list of post-authorization efficacy studies (PAES) imposed as conditions to the marketing authorization or when included as specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances. If no such studies are required, RMP Part IV may be left empty.

5.2.10. RMP part V "Risk minimization measures"

The RMP shall provide details of the risk minimization measures which will be taken to reduce the risks associated with respective safety concerns.

Risk minimization measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient shall adverse reactions occur. Planning and implementing risk minimization measures and assessing their effectiveness are key elements of risk management.

Safety concerns of a pharmaceutical product are normally adequately addressed by routine risk minimization measures. In exceptional cases however, routine risk minimization measures will not be sufficient for some risks and additional risk minimization measures will be necessary to manage the risk and/or improve the risk-benefit balance of a pharmaceutical product.

The need for continuing risk minimization measures shall be reviewed at regular intervals and the effectiveness of risk minimization activities assessed.

Risk minimization measures may consist of routine risk minimization or additional risk minimization measures.

5.2.10.1. Routine risk minimization activities

Routine risk minimization activities are those which apply to every pharmaceutical product. These relate to:

- The summary of product characteristics;
- The labelling;
- The package leaflet;
- The pack size(s);

- The legal status of the product.

Summary of product characteristics (SmPC) and package leaflet (PL)

The summary of product characteristics and the package leaflet are important tools for risk minimization as they constitute a controlled and standardized format for informing healthcare professionals and patients about the pharmaceutical product.

MAH shall accurately revise data included in the RMP (Part V regarding "Routine risk minimization measures" versus its proposed product SPC to include all SPC sections & complete data addressing each corresponding safety concern.

Pack size

Since every pack size is specifically authorized for a pharmaceutical product, planning the number of "dosage units" within each pack and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of "dosage units" shall mean that patients will need to see a healthcare professional at defined intervals, thus increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.

A small pack size can also be useful, especially if overdose or diversion are thought to be major risks.

Legal status

Controlling the conditions under which a pharmaceutical product may be made available can reduce the risks associated with its use or misuse.

This can be achieved by controlling the conditions under which a pharmaceutical product may be prescribed, or the conditions under which a patient may receive a pharmaceutical product.

When a marketing authorization is granted, it shall include details of any conditions or restrictions imposed on the supply or the use of the pharmaceutical product, including the conditions under which a pharmaceutical product may be made available to patients. The conditions under which a pharmaceutical product is made available is commonly referred to as the legal status‖ of a pharmaceutical product.

Typically, it includes information on whether or not the pharmaceutical product is subject to pharmaceutical prescription. It may also restrict where the pharmaceutical product can be administered (e.g. in a hospital, but see below) or by whom it may be prescribed (e.g. specialist).

For pharmaceutical products only available on prescription, additional conditions may be imposed by classifying pharmaceutical products into those available only upon either a restricted medical prescription or a special medical prescription.

5.2.10.2. Additional risk minimization activities

Additional risk minimization activities shall only be suggested when essential for the safe and effective use of the pharmaceutical product. If additional risk minimization activities are proposed, these shall be detailed and a justification of why they are needed provided. The need for continuing with such measures shall be periodically reviewed.

Any educational material shall be non-promotional and any educational program shall be completely separated from promotional activities and contact information of physicians or patients gathered through educational programs shall not be used for promotional activities.

Additional risk minimization measures including:

- Educational programs (Educational tools targeting healthcare professionals and Educational tools targeting patients and/or careers)
- Controlled access programs;
- Other risk minimization measures (Controlled distribution system, Pregnancy prevention program, Direct health care professional communication (DHPC))

Direct health care professional communication (DHPC)

The DHPC **content and the distribution details** shall be submitted to Pharmaceutical Vigilance General Administration (PV GA) - **Emergency safety issue unit** - for **approval prior to distribution**.

The distribution of DHPC starts once approved by Emergency safety issue unit.

After DHPC distribution, progress report shall be submitted (through **compliance follow up portal**) (Affirming the complete distribution of the DHPC to all HCPs included in the list).

Educational material

Any educational material shall **be non-promotional**. It is recommended that communication experts, patients and healthcare professionals are consulted on the design and wording of educational material and that, where appropriate, it is piloted before releasing for use.

Pharmaceutical Vigilance General Administration (PVGA) will agree the key elements of what shall be included in the educational material and these key elements will become, once agreed, a condition of the marketing authorization. In addition, the final version of the educational material will need to be approved by PVGA to check that the material contains the key elements in an appropriate design and format and is not promotional.

For public health reasons, applicants/marketing authorization holders for the same active substance may be required to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorization applicants/holder are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material.

In case the additional risk minimization measure is intended to be distributed to Patient thus; it shall be prepared and submitted in "***Arabic*** ".

The Educational material **content and the distribution details** shall be submitted to Pharmaceutical Vigilance General Administration (PVGA) for **approval prior to distribution**.

The distribution of Educational material starts once approved.

After Educational material distribution, progress report shall be submitted (through **compliance follow up portal**) (Affirming the complete distribution of the Educational material).

For more details and further guidance on additional risk minimization measures is provided in GVP Chapter "Risk minimization measures: selection of tools and effectiveness indicators"

Effectiveness of risk minimization measures

Evaluating the effectiveness of additional risk minimization measures is necessary to establish whether an intervention has been effective or not, and if not why and which corrective actions are necessary. The evaluation shall be performed for the additional risk minimization tools individually and for the risk minimization program as a whole.

Effectiveness evaluation shall be conducted at the most appropriate time, accounting for time required for launch of the risk minimization measures, the estimated use of the product by the healthcare system and other relevant circumstances.

To evaluate the effectiveness of additional risk minimization measures two categories of indicators shall be considered, process indicators and outcome indicators.

If a study to evaluate the effectiveness of risk minimization activities is required, the study shall be included in the pharmacovigilance plan, part III of the RMP.

Guidance on monitoring and evaluation the effectiveness of risk minimization activities and Impact of risk minimization measures effectiveness on RMP/PBRER is included in the Chapter "Risk minimization measures: selection of tools and effectiveness indicators"

5.2.11. RMP part VI "Summary of the risk management plan"

The RMP summary shall be updated when important changes are introduced into the full RMP. Changes shall be considered important if they relate to the following: new important identified or potential risks or important changes to or removal of a safety concern; inclusion or removal of additional risk minimization measures or routine risk minimization activities recommending specific clinical measures to address the risk; major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

The summary of the RMP part VI shall be consistent with the information presented in RMP part II modules SVII, SVIII and RMP parts III, IV and V. It shall contain the following information:

- The pharmaceutical product and what it is authorized for;
- Summary of safety concerns and missing information;
- Routine and additional risk minimization measures;
- Additional pharmacovigilance activities.

5.2.12. RMP part VII "Annexes to the risk management plan"

The RMP shall contain the annexes listed below (if applicable). If the RMP applies to more than one pharmaceutical product, usually it would be expected that the annexes will be relevant for all products. Particular aspects not applicable to all pharmaceutical products in the RMP shall be highlighted (e.g. a follow-up form in annex 4 might only be applicable to the products containing the active substance that is causally linked to the event).

5.2.12.1. RMP annex 1

Annex 1 of the RMP is the structured electronic representation of the risk management plan. This annex can be left empty in the RMP document.

5.2.12.2. RMP annex 2: Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

This annex shall include a tabulation of studies included in the pharmacovigilance plan (current or in previous RMP versions; category 1, 2 and 3 studies), as follows:

- Planned and ongoing studies, including objectives, safety concern addressed, and the planned dates of submission of intermediate and final results.
- Completed studies, including objectives, safety concern addressed, and the date of submission of results to EDA (effective, planned, or state the reason for not submitting the results).

5.2.12.3. RMP annex 3: Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 3 shall not include protocols of studies not imposed nor requested by EDA (i.e. not in the pharmacovigilance plan).

Part A: Requested protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

Part B: Requested amendments of previously approved protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by EDA.

5.2.12.4. RMP annex 4: Specific adverse event follow-up forms

This annex shall include all follow-up forms used by the marketing authorization holder to collect additional data on specific safety concerns. The usage of follow-up forms included in this annex shall be detailed in the pharmacovigilance plan in the RMP, as routine pharmacovigilance activities.

The forms that shall be included in this annex are sometimes known as “event follow-up questionnaire”, “adverse event data capture/collection aid” or “adverse reaction follow-up form”.

5.2.12.5. RMP annex 5: Protocols for proposed and on-going studies in RMP part IV

This annex shall include the protocols for an imposed efficacy study are already included, for studies included in RMP part IV.

5.2.12.6. RMP annex 6: Details of proposed additional risk minimization activities

If applicable, this annex shall include the proposed draft (and approved, if applicable) key messages of the additional risk minimization activities.

5.2.12.7. RMP annex 7: Other supporting data (including referenced material)

All reference documents used to prepare RMP shall be submitted, taking into consideration to attach the full documents (not only the titles - not only the hyperlinks) that was used to define and classify the safety concerns and also documents used to define the risk minimization activity.

5.2.12.8. RMP annex 8: “Summary of changes to the risk management plan over time”

A list of all significant changes to the RMP in chronological order shall be provided in this annex. This shall include a brief description of the changes and the date and version number of the RMPs when:

- Safety concerns were added, removed or reclassified;
- Studies were added or removed from the pharmacovigilance plan;
- Risk minimization activities recommending specific clinical measures to address the risks or additional risk minimization activities were modified in the risk minimization plan.

Quality systems and record management

Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies with the marketing authorization applicant/holder. As such the QPPV shall be aware of, and have sufficient authority over the content. The marketing authorization holder is responsible for updating the RMP when new information becomes available and shall apply the quality principles. The marketing authorization holder shall maintain records of when RMPs were submitted to EDA and the significant changes between RMP versions. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by pharmacovigilance inspectors.

5.3. Operation in Egypt

Risk management has historically focused upon the risk reduction approach and based solely on managing risks. However, when considering how to maximize, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit.

As stated above, the overall aim of risk management is to ensure that the benefits of a particular pharmaceutical product (or a series of pharmaceutical products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. Therefore, although the legal provisions primarily relate to risks, public health will be better served by looking at both benefits and risks, and the regulations include provisions for post-authorization efficacy studies, in addition to post-authorization safety studies, to be a condition of the marketing authorization in certain circumstances.

The requirements above are linked to pharmaceutical products. However, to prevent duplication of planning and resource utilization, there is a possibility for risk management plans to be substance specific. For an individual marketing authorization holder and applicant, all products containing the same active substance shall be included in one RMP unless separate presentations are requested by EDA or agreed by the same at the request of the applicant/marketing authorization holder.

5.3.1. Situations when a risk management plan shall be submitted

A RMP or an update, as applicable, may need to be submitted at any time during a product ‘s life-cycle, i.e. during both the pre- and post-authorization phases.

For all new marketing applications: the risk management plan describing the risk management system which the applicant will introduce for the pharmaceutical product concerned shall be submitted.

Situations, in addition, where a RMP or RMP update will normally be expected include:

- With an application involving a significant change to an existing marketing authorization:
  - New dosage form;
  - New route of administration;
  - New manufacturing process of a biotechnologically-derived product;
  - Pediatric indication;
  - Other significant change in indication;

  A significant change in indication is a change of authorized indication(s) of a pharmaceutical product where the new treatment target population differs materially from the one for which the pharmaceutical product was previously authorized. This includes (but is not limited to): a new disease area, a new age group (e.g. pediatric indication) or a move from severe disease to a less severely affected population. It may also include a move from 2nd line or other therapy or for an oncology product a change to the concomitant medication specified in the indication.

- At the request of EDA when there is a concern about a risk affecting the risk-benefit balance;
- With a submission of final study results impacting the RMP;
- With a PBRER for pharmaceutical product, when the changes to the RMP are a direct result of data presented in the PBRER.
- At the time of the renewal of the marketing authorization if the product has an existing risk management plan.

An updated RMP shall always be submitted if there is a significant change to the benefit-risk balance of one or more pharmaceutical products included in the RMP.

5.3.2. Updates to the risk management plan

If an RMP has previously been submitted by the applicant/marketing authorization holder for the active substance, any following submissions shall be in the form of an update unless requested otherwise. Each submission of the RMP shall have a distinct version number and shall be dated. When technically feasible, clean and track change versions shall be submitted along with a cover letter detailing the changes since the last submitted version.

There are no scheduled "routine" updates to the RMP. In exceptional cases, when justified by risk, EDA may still specify a date for submission of the next RMP as a condition of the marketing authorization.

It is the responsibility of the marketing authorization holder to monitor the safety profile of the product(s) and to update and submit the RMP if there is a significant change to the risk-benefit balance of one or more pharmaceutical products included in the RMP. A significant change would, in particular, usually include extension of indications, clinically important changes to the product information, reaching an important pharmacovigilance milestone and also certain new strengths and formulations.
An updated RMP shall be submitted:

- At the request of EDA;
- Whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the risk-benefit

balance or as a result of an important pharmacovigilance or risk-minimization milestone being reached.

If, when preparing a PBRER, there is a need for consequential changes to the RMP as a result of new safety concerns, or other data, then an updated RMP shall be submitted at the same time. In this case no stand-alone RMP variation is necessary.

Shall only the timing for submission of both documents coincide, but the changes are not related to each other, the RMP submission shall be handled as a stand-alone variation.
When the RMP is updated, the risk minimization plan shall include an evaluation of the impact of routine and/or additional risk minimization activities as applicable.
For MAH/Applicant submitting EU/global RMP & its Egyptian Display; when the referenced EU / global RMP is subject to update the Egyptian Display of RMP shall be updated in accordance.

5.3.3. Implementation of additional risk minimization activities

For products with additional risk minimization activities, it is the responsibility of the marketing authorization holder and EDA to ensure that all conditions or restrictions with regard to the safe use of the product are complied with prior to the authorization of the product.

EDA shall also ensure that any conditions or restrictions with regard to the safe and effective use of authorized product are applied within their territory regardless of the source of the product.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- Safety concerns relating to the active substance;
- Safety concerns related to a specific formulation or route of administration;
- Safety concerns relating to the target population;
- Risks associated with switch to non-prescription status.

Categorization of safety concerns by headings shall only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

5.3.4. Justification for not submitting RMP

The justification for not submitting a RMP shall include the following, **with attached reference documents used in preparing such data**:

- Clear statement that the innovator (patent-holder) has no RMP, with evidence from reference countries on that.
- Table reflecting the updated summary of safety concerns.
- Table reflecting the proposed routine risk minimization activities, and how such routine activities will be sufficient to manage the product safety concerns.
- The proposed SmPC of your product shall be submitted.

Attach all reference documents used to prepare the justification

Note: In case of biological products " Clear statement by the head quarter that the company has no RMP, with the appropriate rational" is required.

5.3.5. Egyptian display for MAH/Applicants having EU/global RMP

Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimization activities will need to be tailored to the system in place. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a pharmaceutical product may also vary between regions. Therefore, a product may need different or supplementary activities in the RMP for each region although there will be core elements which are common to all. For example, much of the safety specification will be the same regardless of where the pharmaceutical product is being used but the epidemiology of the disease may vary between e.g. Africa and Europe, and there may be additional or fewer safety concerns depending upon the target population and indication.

Furthermore, individual countries may have different health systems and medical practice may differ between countries so the conditions and restrictions in the marketing authorization may be implemented in different ways depending upon national customs.

MAH/ Applicants are required to submit RMP taking into consideration that the core elements of the product 's RMP are common and as this guideline was based on the European Good Pharmacovigilance Practice, thus for simplification; MAH/Applicants having EU RMP in place submit the most updated version of the EU RMP (referenced EU RMP including its annexes); altogether with the Egyptian Display of the RMP (including its annexes).

In these circumstances (submitting the Egyptian Display and the EU/Global RMP), the following conditions apply:

- When the referenced EU/Global RMP is subject to update the Egyptian Display of RMP shall be updated in accordance.
- Minor differences may exist between this guidance and the EU/Global RMP, in this case MAH/Applicant may be asked to submit additional information, use different tables, and/or provide clarification…etc.
- The submitted EU/Global RMP shall be the most updated version.
- The EU/Global RMP shall be submitted with its annexes and reference materials
- Generally, it is required that all the risk management activities applied globally/in the EU to be applied in Egypt as well, especially the risk minimization measures including the measurement of their effectiveness. Accordingly, all activities, action plans and details especially the risk minimization ones (including the measurement of their effectiveness) stated in the submitted EU/Global RMP, MAH is required to adhere to them, EXCEPT otherwise clearly stated and justified by the MAH/Applicant in the Egyptian Display of the RMP and agreed by Pharmaceutical vigilance general administration.

The purpose of the "Egyptian Display of the RMP" is:

- To highlight to what extent the risk management activities proposed to be implemented in Egypt adhere to the globally implemented plan and;
- To provide justification for any difference (apart from what implemented in the EU/Globally) whenever exist including the needed national tailoring if any.

- In addition, it shall include an assessment whether there are any additional national/ region-specific risks or not, describing the may be added activities to manage those additional risks.
- It provides good evidence that the LSR/QPPV has clear understanding and commitment about the activities that will be implemented on Egypt and how they will be implemented.

Note:

- In case the EU/Global RMP is available, an Egyptian display of EU/Global RMP **shall be also submitted**
- In case no EU/Global RMP available, a globally signed declaration declaring that **shall be submitted**.

Template of the Egyptian Display of the Risk Management Plan (RMP) for MAH/Applicant having EU/Global RMP refer to Annex III.1

General Notes regarding RMP:

- The RMP is part of the scientific dossier of a product and as such shall be scientifically based and shall not include any element of a promotional nature.
- Any educational program shall be completely separated from promotional activities and contact information of physicians or patients gathered through educational program shall not be used for promotional activities.
- Regular monitoring of the activities of the pharmaceutical products (Routine / additional PV and Risk minimization activities) is required, and once the reference product has any updates on its safety profile, such updates are required to be proposed.
- The documents shall be prepared and reviewed well, to be submitted in a good quality as the quality of the MAH submitted documents reflects MAH performance.
- The RMP document shall be signed by the qualified person for pharmacovigilance (QPPV).
- In case of a non-reference product, MAH shall add data regarding the following modules:
  - *SVI titled "Additional requirements for the safety specification"*
  - *SVII titled "Identified and potential risks"*
- In case of Re-registration and the product is not marketed or launched yet, a statement (on **MAH official paper**) signed by **CEO** declaring that the product is not launched yet and never been marketed or sold by any tenders along with adequate justification is required to be submitted.
- In case of a product subjected to abuse and dependence, Specific analysis for **abuse, misuse and dependence** cases are required be conducted in the PBRERs.
- In case RMP is covering more than one product containing the same active ingredient with (different dosage forms/concentrations), one RMP shall be submitted and the following parts: **Part I, Part VI** and **Annex 3** shall separately represent data of each product (repeated for each pharmaceutical product/concentration).

- The product leaflet shall continuously be updated as per updates of the reference product label in a timely manner.
- In case the product is subjected to additional monitoring:
  - Clarify this in the item "***if your product is subject to additional monitoring***" and include the following in ***the product SPC***:

- **Additional Monitoring Symbol** (Inverted Black Triangle).
- **Additional Monitoring statement:** "*This pharmaceutical product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section ..... for how to report adverse reactions*".

- **All reference documents used to prepare RMP shall be submitted**, taking into consideration to **attach** the **full documents (<u>not only the titles - not only the hyperlinks</u>)** that was used to define and classify the safety concerns and also documents used to define the risk minimization activity , for example –but not restricted to-:

  - Public assessment report
  - The SmPC of the reference product
  - Search results

6. Individual case safety report collection, management, and submission

6.1 Introduction

Individual Case Safety Report (ICSR) chapter refers to the format and content for the reporting of one or several suspected adverse reactions in relation to a pharmaceutical product that occur in a single patient at a specific point of time.

Marketing authorization holders shall take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with pharmaceutical products for human use.

Marketing authorization holders shall report ICSRs to the General Administration of Pharmaceutical Vigilance at EDA.

Reporting adverse reactions by the patients and the healthcare providers is not covered in this chapter. There is a guideline published by EDA for detecting and reporting adverse events Here

6.1.1. Terminology

6.1.1.1. Adverse Event:

Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

6.1.1.2. Adverse Reaction:

A response to a pharmaceutical product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.
Use outside the marketing authorization includes off-label use, overdose, misuse, abuse and medication errors.

6.1.1.3. Day Zero:

It is the first day when EDA or a marketing authorization holder gets knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday.

6.1.1.4. ICH E2B (R2):

E2B R2 is an international standard for transmitting medicine adverse event reports specified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

6.1.1.5. ICH E2B (R3):

ICH E2B (R3) data elements have a hierarchical tree structure. It consists of two major sections A and B, where A contains administrative and identification information, and B contains information on the case. The subsidiary sections are categorized by the nature of the data, and are:

1. Section A
   C.1 - Identification of the Case Safety Report
   C.2 - Primary Source(s) of Information

C.3 - Information on Sender of Case Safety Report
C.4 - Literature Reference(s)
C.5 - Study Identification

2. Section B
D- Patient Characteristics
E- Reaction(s)/ Event(s)
F- Results of Tests and Procedures Relevant to the Investigation of the Patient
G- Drug(s) Information
H- Narrative Case Summary and Further Information

In addition to the letters 'i' and 'k' indicating iterations of the event (E.i) or the drug (G.k), the letter 'r' is used to indicate that the data element or the section is repeatable.

6.1.1.6. Pharmaceutical product:

A pharmaceutical product is characterized by any substance or combination of substances, presented as having properties for treating or preventing disease in human beings; or which may be used in, or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

6.1.1.7. Null Flavors:

The null Flavors are a collection of codes specifying why a valid value is not present in an ICSR. They are available with the ICH-E2B(R3) format and not with ICH-E2B(R2). They refer to instances, where for example a proper value is applicable, but not known (e.g. age of the patient is unknown: code UNK), or where the information is available to a sender of an ICSR but it is masked because it cannot be provided due to security, privacy or other reasons (e.g. date of birth of the patient cannot be shared due to local data protection laws: code MSK).

6.1.1.8. Solicited Report:

Solicited reports of suspected adverse reactions are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare professionals, compassionate use or name patient use, or information gathering on efficacy or patient compliance.

6.1.1.9. Unsolicited Report:

A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to EDA, marketing authorization holder or other organization (e.g. regional pharmacovigilance center, poison control center) that describes one or more suspected adverse reactions in a patient who was given one or more pharmaceutical products.

6.1.2. XML:

XML, or Extensible Markup Language, is a markup language that defines rules for structuring documents in a format that can be read by both humans and machines. The structure of XML is based on a grouping of sections and elements that are annotated by start and end tags. Tags are user-friendly phrases used to indicate the data elements contained within the tags.

For example, using the E2B R2 format a patient's date of birth of 19 March 1972 in XML would appear as: <patient birthdate>19720319</patient birthdates>.

6.2. Structures and processes

The structures and the processes of Individual Case Safety Report collection, management, and submission in Egypt has to be implemented following the Good Pharmacovigilance Practice. This topic explains multiple items that shall be considered in implementation such as: ICSR collection, ICSR validation, ICSR follow-up, data management, quality management, special situations, and finally, the submission of ICSR to EDA.

6.2.1. Processing of ICSR

6.2.1.1. Collection of Individual Case Safety Reports:

EDA and Marketing authorization holders shall collect and collate domestic reports originating from unsolicited or solicited sources.

For locally produced products that are marketed outside Egypt, the MAH shall collect and collate reports from those countries where the product is marketed in, to be reflected in the summary tabulation of the PBRER.

EDA may share serious cases reported from healthcare professionals or consumers regarding specific product, with the relevant Marketing Authorization Holder.

Collected reports shall be authentic, legible, accurate, consistent, verifiable, and as complete as possible for their clinical assessment.

1. Unsolicited Reports

- Spontaneous Reports:
  A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to EDA, marketing authorization holder or other organization (e.g. regional pharmacovigilance center, poison control center) that describes one or more suspected adverse reactions in a patient who was given one or more pharmaceutical product and that does not derive from a study or any organized data collection systems where adverse events reporting is actively sought.
  Stimulated reporting that occurs consequent to a 'Direct Healthcare Professional Communication', publication in the press, questioning of healthcare professionals by company representatives, communication from patients 'organizations to their members, or class action lawsuits shall be considered spontaneous reports.

  Unsolicited consumer adverse reactions reports shall be handled as spontaneous reports irrespective of any subsequent 'medical confirmation'.

- Literature Reports:
  1. The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of pharmaceutical products, particularly in relation to the detection of new safety signals or emerging safety issues.

2. Marketing authorization holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used national and international reference databases (e.g. Medline, Excerpta Medica or Embase) with frequency that shall allow for potential valid ICSRs to be submitted to EDA within the appropriate regulatory submission time frames.
3. The marketing authorization holder shall ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the pharmaceutical product properties19.
4. In addition, marketing authorization holders shall have procedures in place to monitor scientific and medical publications in local journals in countries where pharmaceutical products have a marketing authorization, and to bring them to the attention of the company safety department as appropriate.
5. Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, shall be reviewed and assessed by marketing authorization holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorization studies.
6. Screening and monitoring of reference regulatory authorities' websites for regulatory decisions concerning the MAHs's pharmaceutical product should be done on weekly basis

If multiple pharmaceutical products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction shall be considered by the concerned marketing authorization holder(s).

One case shall be created for each single patient identifiable. Relevant medical information shall be provided and the publication author(s) shall be considered as the primary source(s).

- Reports from non-medical sources:
  If a marketing authorization holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it shall be managed as a spontaneous report.

  Every attempt shall be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR.
  With regard to the submission of those ICSRs, the same modalities and time frames shall be applied as for other spontaneous reports.

- Information on suspected adverse reactions from the internet or digital media:
  Marketing authorization holders shall regularly screen the internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions.

  The frequency of the screening shall allow for potential valid ICSRs to be submitted to EDA within the appropriate regulatory submission time frames based on the date the information was posted on the internet site/digital media. Marketing authorization holders may also consider utilizing their websites to facilitate the collection of reports of suspected adverse reactions.

If a marketing authorization holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report shall be assessed to determine whether it qualifies for submission as ICSR.

The same submission time frames as for spontaneous reports shall be applied.

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the possibility of verification of the existence of a real person based on the information available e.g. an email address under a valid format has been provided.

2. Solicited reports

Solicited reports of suspected adverse reactions are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programs, other patient support and disease management programmes, surveys of patients or healthcare professionals, compassionate use or name patient use, or information gathering on efficacy or patient compliance.

Reports of suspected adverse reactions obtained from any of these data collection systems shall not be considered spontaneous. This is with the exception of suspected adverse reactions originating from certain compassionate use or named patient use where adverse events are not actively sought.

With regard to the submission as ICSRs, solicited reports shall be classified as study reports. They shall have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria.

ICSRs shall be submitted in line with the time frames and modalities.

6.2.1.2. Validation of ICSRs:

Only valid ICSRs shall be reported. So, all reports of suspected adverse reactions shall therefore be validated before submitting them to EDA to make sure that the minimum criteria for reporting are included, which are:

One or more identifiable reporter

Characterized by parameters such as qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional), name, initials, or address (e.g. reporter's organization, department, street, city, state or province, postcode, country, email, phone number). Local data protection laws might apply.

Contact details for the reporter shall be recorded to facilitate follow-up activities. However, if the reporter does not wish to provide contact information, the ICSR shall still be considered valid as long as the notified organization is able to confirm the case directly with the reporter.

To enable duplicate detection activities, all parties providing case information or approached for case information shall be recorded in the ICSR (not only the initial reporter).

An ICSR is not valid for submission unless information concerning the qualification and the country is available for at least one reporter.

One single identifiable patient

Characterized by at least one of the following: initials, medical record number {from a general practitioner, specialist, hospital, or investigation}, date of birth, age, age group, gestation period, or gender.

The term 'identifiable' refers to the possibility of verification of the existence of a patient based on the available information.

One or more suspected substance/pharmaceutical product

Interacting substances or pharmaceutical products shall also be considered suspected.

One or more suspected adverse reactions.

If the primary source has made an explicit statement that a causal relationship between the pharmaceutical product and the reported adverse event has been excluded and EDA or a marketing authorization holder agrees with this assessment, the report does not qualify as a valid ICSR since the minimum information for validation is incomplete (there is no suspected adverse reaction).

The report also does not qualify as a valid ICSR:

- If it is reported that the patient experienced an unspecified adverse reaction and there is no information on the type of adverse reaction.
- If only an outcome (or consequence) is notified and
  i. No further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or
  ii. The primary source has not indicated a possible causal relationship with the suspected pharmaceutical product.

For instance, a marketing authorization holder is made aware that a patient was hospitalized or died, without any further information. In this particular situation, medical judgement shall always be applied in deciding whether the notified information is an adverse reaction or an event.

For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and the valid ICSR shall be submitted.

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR.

EDA and marketing authorization holders are expected to exercise due diligence in following-up the case to collect the missing data elements and follow-up activities shall be documented. Reports, for which the minimum information is incomplete, shall be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.

A valid case of suspected adverse reaction initially notified by a consumer cannot be downgraded to a report of non-related adverse event if a contacted healthcare professional (nominated by the consumer for follow-up information) subsequently disagrees with the consumer's suspicion. In this situation, the opinions of both the consumer and the healthcare professional shall be detailed in the narrative section of the ICSR.

Similarly, a solicited report of suspected adverse reaction shall not be downgraded to a report of non-related adverse event, when the notified recipient (EDA or marketing authorization holder) disagrees with the reasonable possibility of causal relationship expressed by the primary source on

the supplied pharmaceutical product. The opinions of both, the primary source and the recipient, shall be recorded in the narrative section of the ICSR.

In addition to the previous mandatory elements, an ICSR shall contain the following:

1. Case ID/ Manufacture control number
2. Date of report (initial report date): when the report was first recorded by the initial reporter
3. MAH details (name and address)
4. Case narrative

6.2.1.3. Follow-up of reports (if needed)

When first received, the information in suspected adverse reactions reports may be incomplete. These reports shall be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.

This is particularly relevant for monitored events of special interest, prospective reports of pregnancy cases notifying the death of a patient, or cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum criteria for reports validation.

Follow-up methods shall be tailored towards optimizing the collection of missing information. This shall be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern.

The use of targeted specific forms in the local language shall avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting.

Significant information

Marketing authorization holders shall submit follow-up ICSRs if significant new medical information has been received.

Significant new information relates to, for example, a new suspected adverse reaction, a change in the causality assessment, and any new or updated information on a case that impacts on its medical interpretation. Medical judgement shall therefore be applied for the identification of significant new information requiring to be submitted as follow-up ICSR.

Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g., the follow-up information leads to a change of the seriousness criteria from serious to non-serious, or the causality assessment is changed from related to non-related) shall also be considered as significant changes and thus submitted as ICSR.

In addition, the marketing authorization holder shall also submit a new version of an ICSR, when new administrative information is available, that could impact on the case management. For example, if new case identifiers have become known to the sender, which may have been used in previous submissions. This information may be specifically relevant to manage potential duplicates.

N.B.

In each submission, the date of receipt of the most recent information, the worldwide unique case identification number and the sender's identifier are required.

When additional significant information is received for a previously submitted case, the clock for the submission of a follow-up report starts again from the date of receipt of the relevant follow-up information.

Non-significant information

In contrast, a follow-up report which contains non-significant information does NOT require to be submitted as ICSR. This may refer, for example, to minor changes to some dates with no implication for the evaluation or submission of the case, or to some corrections of typographical errors in the previous case version.

Medical judgement shall be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient). Similarly, a change of the status of a MedDRA code/term from current to noncurrent, due to a version change of MedDRA, can be considered as a non-significant change as long as this change has no impact on the medical content of a case.

N.B.

Any attempt to collect missing data elements and obtain follow-up information shall be documented and kept at the marketing authorization holder registries.

Priority Levels for Follow-up:

Priority 1: Serious unexpected reports and serious reports associated with possibly action requiring events (such as suspected falsified/ counterfeit medicine, suspected quality defects, medication errors, lack of efficacy, abuse, misuse, or occupational exposure).

Serious AEFIs are always considered priority 1.

Priority 2: Serious expected reports and non-serious reports associated with possibly action requiring events (such as suspected falsified/counterfeit medicine, suspected quality defects, medication errors, lack of efficacy, abuse, off-label use, misuse, or occupational exposure)

Priority 3: Non serious reports (expected or unexpected), which are not associated with action requiring events.

6.2.1.4. Medical Confirmation

A consumer may provide medical documentations (e.g. laboratory or other test data) that support the occurrence of a suspected adverse reaction and which indicate that an identifiable healthcare professional suspects a causal relationship between a pharmaceutical product and the reported adverse reaction. Similarly, a report may be notified by a medically qualified patient, friend, relative or carer of the patient. In these situations, the reported information is considered medically confirmed.

In the same way, where one or more suspected adverse reactions initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR shall be considered medically confirmed.

6.2.1.5. MedDRA Coding:

The Medical Dictionary for Regulatory Activities (MedDRA) shall be used at the lowest level term (LLT) in the ICSRs.
The MedDRA LLT term corresponding most closely to the reported information shall be added to the observed suspected adverse reaction(s), in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users.
When MedDRA terms are used, the MedDRA version number shall be provided.

6.2.1.6. Seriousness Assessment

A serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The characteristics/consequences shall be considered at the time of the reaction to determine the seriousness. For example, life-threatening refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical judgement shall be exercised in deciding whether other situations shall be considered serious. Some medical events may jeopardize the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events shall be considered serious.

An important medical event (IME) terms list (available on EMA website) aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of ICSRs in the framework of the pharmacovigilance activities. The IME list is intended for guidance purposes only to stakeholders who wish to use it for their pharmacovigilance activities. It is regularly updated in line with the latest version of MedDRA.

6.2.1.7. Causality Assessment

The degree of suspected relatedness of each pharmaceutical product to each reported adverse reaction shall be presented in a structured manner in the ICSR.

It can be expressed for multiple sources (reporters, EDA, marketing authorization holders) while using multiple methods of causality assessment.

Preferred used methods for causality assessment:

- WHO-UMC
- WHO-AEFI (for vaccines)

6.2.1.8. Data Entry in the Database

The received valid ICSRs (serious and non-serious) are entered into the national database Vigiflow, which is a web-based pharmacovigilance management system with streamlined easy-to-follow workflows that uses integrated standardized medical terminologies such as WHO Drug Global and MedDRA.

6.2.1.9. Duplicate Reports

A duplicate refers to the same individual case reported by a primary source to describe suspected adverse reaction(s) related to the administration of one or more pharmaceutical products to an individual patient at a particular point of time. This individual case may be reported by different senders, through different routes, whereby the case information may be handled differently by the processor of the case, which makes it difficult to identify the reported cases as duplicates. Case handling refers for example to coding practices, obtaining follow-up information and processing of personal data.

The presence of duplicates in any pharmacovigilance database can create misleading signals and therefore impact on the safe ty monitoring and potential regulatory actions.

Examples of common causes of duplicate reports are:

- A consumer and a healthcare professional reporting the same reaction occurrence
- Multiple health care professionals treating the same patient reporting the same reaction occurrence
- A reaction occurrence being reported by the original reporter to both the marketing authorization holder and EDA.
- Literature reporting of the same reaction occurrence for generics.

Handling duplicate reports typically involves three steps:
(1) searching/detection of duplicates
(2) confirmation of duplicates
(3) management of duplicates

Detection of duplicate cases:
Databases shall be reviewed regularly to identify duplicates. Screening for duplicates shall be done at the time when a new report arrives in the database i.e. during data entry or during the process of loading ICSRs that have been received electronically.

Duplicate searches are generally based on similarities in patient, adverse reaction and pharmaceutical product data. Different search criteria may be suitable for different datasets.

For pharmacovigilance systems that do not have to deal with large datasets, a simple table which sorts the reports by age, sex, suspected/ interacting pharmaceutical products and adverse reactions can be suitable to detect similarities.
A search for duplicates can be based on the MedDRA Preferred Term (PT) Level, but moving up to the associated Higher Level Term (HLT) or even HLGT (Higher Level Group Term (HLGT) might be appropriate.

Management of duplicates cases:
Duplicate cases are generally managed through a process of merging two or more cases into one master case.

This process can consist of one of the following approaches:

- The master case can either be based on one of the existing cases, with information from the other subordinate duplicate cases added unless the same, or more precise, information is already present in the master case (Allocation of a master case),

or;

- The master case can be created as a new case combining the information from the subordinate duplicate cases (Creation of a master case).

Regardless of the approach chosen, the master case shall always contain all case reference numbers from all subordinate duplicate cases, such that they can be easily traced. The master case shall reflect the most accurate and up-to-date information available to the organization.

Both concepts are acceptable; however, whatever method chosen, the process shall be well documented.
Proper record management shall ensure that all received ICSRs for all individual cases can be tracked adequately, including all information as reported by the primary sources, the reporters and the report senders. The "Date report was first received from source" and "Date of receipt of the most recent information for this report" of the duplicates shall remain unchanged unless new information is received.
The case narrative shall reflect information from both sources.

6.2.1.10. Case narrative

In Egypt, all the submitted ICSRs shall be provided with a detailed case narrative containing all detailed information regarding the case. The information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained.
The case narrative shall serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the events, diagnoses, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions.
With regard to the identifiability of the patient, information shall be provided in accordance with local data protection laws.

6.2.1.11. Signal Detection

When the ICSR is stored in the national database "Vigiflow", it is available for signal detection and data quality analyses following recoding and duplicate detection.

6.2.1.12. Risk/ Benefit Evaluation

Events/ observations may occur in relation to an authorized pharmaceutical product, which may have major impacts on the risk-benefit balance of the product and/or on patients or public health. They may require urgent attention of EDA and could warrant prompt regulatory action and communication to patients and healthcare professionals.
These important new evidences shall be considered as emerging safety issues. They shall be notified to EDA; this is in addition to the ICSR submission when the emerging safety issue refers to a single case of suspected adverse reactions.

6.2.1.13. Safety Communication regarding ICSRs

Aims of Safety communication of ICSRs:

- Providing timely, evidence-based information on the safe and effective use of medicines;
- Facilitating changes to healthcare practices (including self-medication practices) where necessary;
- Changing attitudes, decisions and behaviors in relation to the use of medicines;
- Supporting risk minimization behavior;
- Facilitating informed decisions on the rational use of medicines. In addition to the above effective, high-quality safety communication can support public confidence in the regulatory system.

Means of safety communication

- Direct healthcare professional communication (DHPC)
- Communication materials from EDA targeted at healthcare professionals
- Documents in lay language to patients and the general public
- Press communication
- Website
- Social media and other online communications
- Bulletins and newsletters
- Inter-authority communication
- Responding to enquiries from the public
- Other means of communication, such as publications in scientific journals and journals of professional bodies.

6.2.2. Submission of ICSRs

6.2.2.1. Reception of ICSRs

The marketing authorization holder shall submit all ICSRs that occur in Egypt (i.e. domestic ICSRs) to the General Administration of Pharmaceutical Vigilance.

ICSRs shall be submitted electronically as structured data as XML format (preferably) in the form of E2B (R2) or E2B (R3).

Also, CIOMs form (pdf) may be accepted in circumstances where there is a problem in submitting in XML format. These circumstances are:

1. If the company is still in the process of developing a database that creates the required XML files.
2. If there is a technical problem in the company's database.
3. If the time required to prepare the XML file will result in exceeding the timeframe required for the submission of the report.

Pharmaceutical companies shall report ICSRs through:

- E-mails to: pv.report@edaegypt.gov.eg

- Uploading their cases on the specific link of Pharmaceutical Vigilance General Administration Reporting Portal as defined in the operational procedures' manual on EDA website.

6.2.2.2. Submission Time frames for ICSRs

The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of any personnel of the marketing authorization holder, including medical representatives and contractors. This date shall be considered as day zero.

When additional significant information is received for a previously reported case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow-up information.

Serious ICSRs	Serious valid ICSRs shall be reported to the General Administration of Pharmaceutical Vigilance by marketing authorization holders within **15 days** from the date of receipt of the reports.
Non-serious ICSRs	Non-serious valid ICSRs shall be reported to the General Administration of Pharmaceutical Vigilance by marketing authorization holders within **90 days** from the date of receipt of the reports.
Special situations	In some special situations, another time frame for submitting individual reports of the adverse effects shall be followed and MAHs shall adhere to the specified time frame. As in case of reporting of pharmaceutical products under "Emergency Use Authorization (EUA)": Pharmaceutical companies shall collect and **notify** adverse reactions from vaccines under Emergency Use Authorization (EUA) to the General Administration of Pharmaceutical Vigilance as following: **Serious case**: within **24 hours**. **Non serious case**: within **7 days**. Submission of the final report after validation in a time frame no longer than 15 days.

6.2.3. Report Amendment

There may be instances, where an ICSR which has already been submitted may need to be amended, for example when, after an internal review or according to an expert opinion some items have been corrected (such as adverse event/ reaction terms, seriousness, seriousness criteria or causality assessment) but without receipt of new information that would warrant submission of a follow-up report.

The same would apply where documentations mentioned in an ICSR, translations or literature articles are requested by EDA and are further sent as attachments in line with ICH E2B(R3). These submissions are considered as amendment reports.

6.2.4. Report Nullification

The nullification of ICSRs shall be used to indicate that a previously transmitted report shall be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports.

The process of the nullification of a case is by means of a notification by the pharmaceutical company to the General Administration of Pharmaceutical Vigilance, that this is no longer a valid case.

The nullification reason shall be clear and concise to explain why this case is no longer considered to be a valid report.

It is essential to use the same case report number (report ID) previously submitted.

However, the case shall be retained in the sender‘s pharmacovigilance database for auditing purposes.

6.2.5. Special situations

6.2.5.1. Use of a pharmaceutical product during pregnancy or breastfeeding

These cases shall be reported as following:

a. If the child/ fetus experiences suspected adverse reactions (other than early spontaneous abortion/ fetal demise):

- When the child or fetus, exposed to one or several pharmaceutical products through the parent, experiences one or more suspected adverse reactions other than early spontaneous abortion/fetal demise, information on both the parent and the child/fetus shall be provided in the same report.
- The case is referred to as a “parent-child/fetus report”.
- The patient’s characteristics applies only to the child/fetus.
- The characteristics concerning the mother or father, who was the source of exposure to the suspect pharmaceutical product, shall be captured as part of the information concerning the parent.
- If both parents are the source of the suspect drug(s), the structured parent information in the case shall reflect the mother’s characteristics; information regarding the father shall be provided in the narrative together with all other relevant information.

b. If both the parent and child/fetus experience suspected adverse reactions:

When the parent and the exposed child/ fetus experience suspected adverse reactions other than early spontaneous abortion/fetal demise, two separate reports, i.e., one for the parent (mother or father) and one for the child/fetus, shall be created.

Both reports shall be linked.

c. If no reaction is affecting the child/fetus:

When no reaction is reported for the exposed child/fetus, the parent-child/fetus report does NOT apply.

An Individual Case Safety Report is submitted in the following situations of Maternal Exposure such as:

- Reports of congenital anomalies or developmental delay in the foetus or the child
- Reports of fetal death and spontaneous abortion
- Reports of suspected adverse reactions in the neonate that are classified as serious
- Maternal exposure with other ADR
- Contraindicated drugs
- Maternal exposure occurred with other ADRs
- Maternal exposure to pharmaceutical products contraindicated in pregnancy

Unless requested by EDA, other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome shall not be submitted as ICSRs since there is no suspected adverse reaction. This data is reflected in the PBRER specified section.

d. If miscarriage or early spontaneous abortion is reported:

When miscarriage or early spontaneous abortion is reported, only a parent report is applicable with the patient's characteristics to be provided for the mother.

However, if the suspect pharmaceutical product was taken by the father, this information shall also be recorded.

6.2.5.2. Use of a pharmaceutical product in a pediatric or elderly population

The collection of safety information in the paediatric or elderly population is important. Reasonable attempts shall therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population.

6.2.5.3. Reports of overdose, abuse, misuse, medication error or occupational exposure

Reports with no associated suspected adverse reaction shall not be submitted as ICSRs. They shall be recorded when becoming aware of them and considered in the periodic safety update reports as applicable.
When those reports constitute safety issues impacting on the risk- benefit balance of pharmaceutical products, they shall be notified to EDA.

Reports associated with suspected adverse reactions shall be subject to submission. They shall be routinely followed-up to ensure that the information is as complete as possible with regard to the symptoms, suspected pharmaceutical products name, outcomes, context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorized indication or population, etc.).

6.2.5.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy shall be collected and recorded when notified and followed-up if incomplete. They shall normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they shall be discussed in periodic safety update reports as applicable.

In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame. For example, pharmaceutical products used in critical conditions or for the treatment of life- threatening diseases, vaccines and contraceptives.
This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the pharmaceutical product.

The requirement to submit these specific reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional post-authorization efficacy study. This is because they refer to the main end point of the study.

Clinical judgement shall be used when considering if cases of lack of therapeutic efficacy qualify for submission as ICSRs. For example, a report of lack of therapeutic efficacy with an antibiotic used in a life-threatening situation where the use of the pharmaceutical product was not in fact appropriate for the infective agent shall not be submitted. However, a report of lack of therapeutic efficacy for a life-threatening infection, which appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, shall be submitted as ICSR within 15 days.

For vaccines, cases of lack of prophylactic efficacy shall be submitted as ICSRs, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of prophylactic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post- authorization safety studies as appropriate.

6.2.5.5. Suspected adverse reaction reports published in the medical literature

With regard to the electronic submission of ICSRs published in the medical literature, the following applies:

- The literature references shall be included in the data element “Literature reference(s)” in the Vancouver Convention (known as “Vancouver style”), developed by the International Committee of Medical Journal Editors.
- A comprehensive English summary of the article shall be provided in the “case narrative” including clinical course, therapeutic measures, outcome and additional relevant information.
- Upon request of EDA, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorization holder that transmitted the initial report, taking into account copyright restrictions.
- The electronic version of the document (i.e. the journal article and a copy of the translation where applicable) shall be attached to the ICSR in data element C.4.r.2 ‘Included Documents’.

- If the article and/or translation are not provided at the time of the ICSR submission, attachments can be transmitted separately. In this situation, the original ICSR along with all the same medical information captured in the E2B(R3) data elements shall be retransmitted as an 'amendment' report. However, if new additional information is provided, then the ICSR with the attachment shall be submitted as a follow-up report.

Along with the resulting suspected adverse reactions, an appropriate MedDRA LLT term corresponding most closely to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure shall be specified in the ICH-E2B section 'Reactions/Events'. This shall be done in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users.

- As a general principle, additional characteristics related to the medicines and pertinent to the case shall be coded and further information provided.
- Data element 'pharmaceutical product name' shall be completed in accordance with the information reported by the primary source.
- Data element 'Additional information on drug' can be used to specify any additional information pertinent to the case (e.g., overdose, medication error, misuse, abuse, occupational exposure, off-label use). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element 'Indication for use in the case'.
- An appropriate MedDRA terms shall be provided for the drug characterization in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction. If applicable, the data element 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' shall be completed with a reasoning provided in the data element 'Sender's comments.
- If the primary source did not provide an explicit statement about the overdose, medication error, misuse, abuse, occupational exposure or off-label use, which would clearly transpose into a MedDRA term in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)', but there is a suggestion in the context of the clinical course description, the sender may provide that information in the data element 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' with a reasoning provided in the data element 'Sender's comments'. The case shall be followed up to obtain further information.

6.2.5.6. Suspected adverse reactions related to quality defect or falsified pharmaceutical products

Quality defect

Where a report of suspected adverse reactions is associated with a suspected or confirmed quality defect of a pharmaceutical product, the MedDRA LLT term corresponding most closely to the product quality issue, shall be added to the observed suspected adverse reaction(s) in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users.

Data element 'Additional information on drug' shall be used to specify any additional information pertinent to the case (e.g., beyond expiration date, batch and lot tested and found to be within/not within specifications). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element 'Indication for use in the case'.

An appropriate MedDRA term shall be provided for the drug characterization in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction.

If applicable, the data element 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' shall be completed with a reasoning provided in the data element 'Sender's comments.

It is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted ICSR.

Falsified pharmaceutical products

Where a report of suspected adverse reactions is associated with a suspected or confirmed falsified excipient, active substance or pharmaceutical product, the MedDRA LLT term corresponding most closely to the reported information shall be added to the observed suspected adverse reaction(s) in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users.

Information on the suspected pharmaceutical product, active substance(s) or excipient(s) shall be also provided.

- As a general principle, additional characteristics related to the medicines and pertinent to the case shall be coded and further information related to the falsified pharmaceutical product provided in free text.
- 'Proprietary pharmaceutical product name' shall be populated in accordance with the information reported by the primary source.
- 'Additional information on drug' shall be used to specify any additional information pertinent to the case (e.g. falsified medicine, medicine purchased over the internet). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element 'Indication for use in the case'.
- An appropriate MedDRA term shall be provided for the drug characterization in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction.
- If applicable, the data element 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' shall be completed with a reasoning provided in the data element 'Sender's comments.
- If new information is received to confirm the product is not a counterfeit, the data element 'Additional information on drug' shall be changed appropriately in a follow-up.
- If the product is confirmed as a counterfeit, the appropriate MedDRA code shall be used in the data element 'Sender's diagnosis with a reasoning provided in the data element 'Sender's comments and information shall be provided in the case narrative.

6.2.5.7. Suspected transmission via a pharmaceutical product of an infectious agent

The coding of a suspected transmission of an infectious agent via a pharmaceutical product shall be performed in line with the latest version of the Guide for MedDRA Users.

In addition, if the infectious agent is specified in the report, the MedDRA LLT term corresponding most closely to the infectious agent shall also be included in the ICSR.

The appropriate MedDRA term shall be provided in the data element ‘Reaction/event in MedDRA terminology (Lowest Level Term)’.

6.2.5.8. Reports of suspected adverse reactions originating from organized data collection systems and other systems

Individual reports originating from post-authorization studies shall contain information on study type, study name and the sponsor’s study number or study registration number. This shall be provided in ICH E2B(R2) section A.2.3 ‘Study identification’.

All ICSRs which originate from organized data collection systems and other systems, shall be submitted to EDA.

The following submission rules for ICSRs shall be applied based on:

- The type of data collection system, and
- Whether the suspected pharmaceutical product is part of the scope of the data collection system.

1. **For all patient support programs, non-interventional studies with primary data collection from consumers and healthcare professionals, and for certain compassionate use or named patient use where adverse events are actively sought:**
   a) Where the adverse reaction is suspected to be related at least to the studied (or supplied) pharmaceutical product:

   - The report shall be considered solicited.
   - The ICH E2B(R2) data element A.1.4 'Type of report' shall be populated with the value 'Report from study';
   - The ICH E2B(R2) data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' shall be populated with the value ‘Other studies’ or 'Individual patient use'.

   b) Where the adverse reaction is only suspected to be related to a pharmaceutical product which is not subject to the scope of the organized data collection system and there is no interaction with the studied (or supplied) pharmaceutical product:
   - The report shall be considered as spontaneous report; as such it conveys the suspicion of the primary source;
   - The ICH E2B(R2) data element A.1.4 'Type of report' shall be populated with the value 'Spontaneous'.
2. **For certain compassionate use or named patient use where adverse event reporting is not solicited:**
   - The report shall be considered as spontaneous report; as such it conveys the suspicion of the primary source;
   - The ICH E2B(R2) data element A.1.4 'Type of report' shall be populated with the value 'Spontaneous'.

3. **For clinical trial and where the adverse reaction is only suspected to be related to a non-investigational pharmaceutical product (or another pharmaceutical product which is not subject to the scope of the clinical trial) and there is no interaction with the investigational pharmaceutical product:**
    - The report shall be considered as spontaneous report; as such it conveys the suspicion of the primary source
    - The ICH E2B(R2) data element A.1.4 'Type of report' shall be populated with the value 'Spontaneous'.

6.2.5.9. Receipt of missing minimum information

When missing minimum information has been obtained about a non-valid ICSR, the following rules shall be applied:

- The data element 'Date report was first received from source'(ICH-E2B(R2) A.1.6) shall contain the date of receipt of the initial non-valid ICSR;
- The data element 'Date of receipt of the most recent information for this report'(ICH-E2B(R2) A.1.7) shall contain the date when all the four elements of the minimum information required for reporting have become available;
- Clarification shall be provided in the case narrative (data element ICH-E2B(R2) B.5.1) that some of the four elements were missing in the initial report;
- As for any reported cases, compliance monitoring is performed against the data element 'Date of receipt of the most recent information for this report'(ICH-E2B(R2) A.1.7).

6.3. Operation in Egypt

This section highlights Egypt`s specific requirements in relation to the collection, management and reporting of reports of suspected adverse reactions (serious and non-serious) associated with pharmaceutical products for human use authorized in Egypt, independently of their condition of use.

Regarding clinical trials, the General Administration of Clinical Trials under the Central Administration of Biological and Innovative Products and Clinical Studies, responsible for the reports from clinical trials.

6.3.1. Marketing Authorization Holders roles and responsibilities:

- ICSRs collection
- ICSRs reporting and submission to EPVC (via e-mail to pv.report@edaegypt.org or via the Reporting Portal)
- Quality and Archiving
- Documentation of the ICSRs
- Checking for Duplicates
- Medical confirmation (for the reports from consumers)
- MedDRA coding and Compliance
- Interface with Emerging Safety Issues and collective summary tabulation in PBRER.
- The reports with problems as (off-label use, misuse, abuse, medication error, etc….) shall be summarized in PBRER

6.3.2. EDA roles and responsibilities:

- EDA shall have in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or marketing authorization holders. In this context, EDA shall establish procedures for collecting and recording all reports of suspected adverse reactions that occur in their territory. The general principles together with the reporting modalities shall be applied to those reports.
- The retention of pharmacovigilance data and documents relating to patient (especially ICSRs, etc.) shall be kept lifelong. However, the documents shall be retained for a longer period where national law so requires.
- EDA shall take all appropriate measures to encourage healthcare professionals and consumers to report suspected adverse reactions.
- EDA shall facilitate the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and consumers, in addition to web-based formats. Information on the different ways of reporting suspected adverse reactions related to pharmaceutical products, shall be made publicly available including by means of national medicines web-based portals (official websites). To increase awareness of the reporting systems, organizations representing consumers and healthcare professionals may be involved as appropriate.
- EDA shall develop standard web-based structured forms and mobile application, when applicable, for the reporting of suspected adverse reactions by healthcare professionals and consumers in order to collect -across Egypt- harmonized information relevant for the evaluation of suspected adverse reactions, including errors associated with the use of pharmaceutical products.
- The reports of suspected adverse reactions received from healthcare professionals and consumers shall be acknowledged where appropriate and further information shall be provided to the reporters as requested and when available.
- If there are justifiable grounds resulting from pharmacovigilance activities on the Egyptian level, EDA may impose additional obligations on marketing authorization holders for the reporting of suspected adverse reactions.
- EDA participating in the WHO Program for International Drug Monitoring shall report to the WHO Collaborating Centre for International Drug Monitoring all suspected adverse reactions reports occurring in their territory. This will take place on a weekly basis after their transmission to the ―National Pharmacovigilance and Safety reports database. Another frequency may be adopted by the General Administration of Pharmaceutical Vigilance as appropriate.

6.3.3. Electronic exchange of safety information:

For the classification, description, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and pharmaceutical product information, EDA and marketing authorization holders shall apply the hereafter "internationally agreed terminology" and "internationally agreed formats and standards".

<u>Use of internationally agreed terminology</u>

- ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA);

- The terminology set out in EN ISO 11615:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated pharmaceutical product information '(ISO/FDIS 11615:2012);
- The terminology set out in EN ISO 11616:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated pharmaceutical product information '(ISO/FDIS 11616:2012);
- The terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on substances '(ISO/FDIS 11238:2012);
- The terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration '(ISO/FDIS 11239:2012);
- The terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of units of measurement '(ISO/FDIS 11240:2012).

Use of internationally agreed formats and standards

- ICH E2B(R2): Maintenance of the ICH guideline on clinical safety-data management: Data elements for transmission of individual case safety reports. While the implementation of ICH-E2B(R3) is being prepared for, ICH-E2B(R2) remains the currently applicable format for transmission of individual case safety reports;
- ICH M2 standard _Electronic Transmission of Individual Case Safety Reports Message Specification '.
- EN ISO 27953-2:2011 Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR (ISO 27953-2:2011);
- EN ISO 11615:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated pharmaceutical product information '(ISO/FDIS 11615:2012);

- EN ISO 11616:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated pharmaceutical product information '(ISO/FDIS 11616:2012);
- EN ISO 11238:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on substances '(ISO/FDIS 11238:2012);
- EN ISO 11239:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration '(ISO/FDIS 11239:2012);

- EN ISO 11240:2012, Health Informatics, Identification of Pharmaceutical Products (IDMP) standard, _Data elements and structures for unique identification and exchange of units of measurement '(ISO/FDIS 11240:2012).EN L 159/14 Official Journal of the European Union 20.6.2012
- In addition, the following guidelines shall be applied:
  - MedDRA Term Selection: Points to Consider Document - The latest version of the
  - ICH-endorsed Guide for MedDRA Users;
  - ICH E2B (R5) Implementation Working Group - Questions & Answers (March 3, 2005);
  - The ICH-M5 guideline _Routes of Administration Controlled Vocabulary '
  - (CHMP/ICH/175860/2005), which provides standard terms for routes of administration;
  - The latest version of these documents shall always be considered.

7. Periodic Benefit Risk Evaluation Report (PBRER)

7.1. Introduction

Periodic Benefit Risk Evaluation Report (PBRER), previously known as periodic safety update reports (PSUR), is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a pharmaceutical product for submission by marketing authorization holders at defined time points during the post-authorization phase.
This Chapter provides guidance on the preparation, submission and assessment of PSURs.

The scope, objectives, format and content of the PBRER are described **under 7.2 "Structures and processes".** The required format and content of PBRERs in Egypt are based on those for PBRER described in the European Good Pharmacovigilance Practice as well as for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline. The PBRER format replaces the PBRER format previously described in the ICH-E2C(R1).

Further details and guidance for the submission of PBRERs in Egypt, including the list of references dates and frequency of submission are provided in **under 7.3 "Operation and Implementation in Egypt"**. As this guideline was based on the European Good Pharmacovigilance Practice; the "list of EU reference dates" is adopted in this guideline as well. Hence, the PBRERs submitted in Egypt shall follow the dates & frequency stated in the most updated version of that list, despite this, EDA may request the submission of PBRERs at any time or to change as appropriate the submission frequency on the national level.

Each marketing authorization holder shall be responsible for submitting PBRERs for **ALL** its own products once a license is granted according to the following timelines:

- Within 70 calendar days of the data lock point (day 0) for PBRERs covering intervals up to 12 months (including intervals of exactly 12 months); and
- Within 90 calendar days of the data lock point (day 0) for PBRERs covering intervals in excess of 12 months;
- For ad hoc PBRERs (requested by EDA): the timeline for submission will be specified in the request; otherwise, ad hoc PBRERs shall be submitted within 90 calendar days of the data lock point.

The above stated submission timelines shall not be exceeded otherwise this will be considered a deviation / non-compliance.

It shall be noted that detailed listings of individual cases shall not be included systematically. The PBRER shall focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.
The obligations imposed in respect of PBRERs shall be proportionate to the risks posed by pharmaceutical products. PBRER reporting shall therefore be linked to the risk management systems of a pharmaceutical product (see chapter 5). The "modular approach" of the PBRER aims to minimize duplication and improve efficiency during the preparation and review of PBRERs along with other regulatory documents such as the safety specification in the Risk Management Plan (RMP), by enabling the common content of particular sections where appropriate to be utilized interchangeably across different PBRERs and RMPs.

In order to avoid duplication of efforts and to prioritize the use of limited resources, a single assessment of PBRERs for different authorized pharmaceutical products containing the same active substance or the same combination of active substances shall be performed.

As part of the assessment, it shall be considered whether further investigations need to be carried out and whether any action concerning the marketing authorization of products containing the same active substance or the same combination of active substances, and their product information is necessary.
PBRERs for generic pharmaceutical products, well-established use pharmaceutical products, homeopathic pharmaceutical products and traditional herbal pharmaceutical products are required to be submitted in the Egypt (unless otherwise is announced by EDA).

Relationship between PBRER and risk management plan

During the preparation of a PBRER, the marketing authorization holder shall consider whether any identified or potential risks discussed within the PBRER is important and requires an update of the RMP.

In these circumstances, updated revised RMP including the new important safety concern shall be submitted with the PBRER and assessed in parallel.

If important safety concerns are identified by the authority during the assessment of a PBRER and no updated RMP or no RMP has been submitted, recommendations shall be made to submit an update or a new RMP within a defined timeline.

PBRER and risk management plan – common chapters:

The proposed modular formats for the PBRER and the RMP aim to address duplication and facilitate flexibility by enabling common PBRER/RMP sections to be utilized interchangeably across both reports. Common sections with the above-mentioned reports are identified in the following table:

PBRER section	RMP section
Section 3 – "Actions taken in the reporting interval for safety reasons"	Part II, chapter SV – "Post-authorization experience", section "Regulatory and marketing authorization holder action for safety reason"
Sub-section 5.2 – "Cumulative and interval patient exposure from marketing "experience	Part II, chapter SV – "Post-authorization experience", section "Non-study post-"authorization exposure
Sub-section 16.1 – "Summary of safety concerns"	Part II, chapter SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PBRER reporting interval)

Sub-section 16.4 – "Characterization of risks"	Part II, Chapter SVII – "Identified and potential risks"
Sub-section 16.5 – "Effectiveness of risk minimization (if applicable)	Part V – "Risk minimization measures", section "Evaluation of the effectiveness of risk minimization activities

7.2. Structures and processes

7.2.1. Objectives of the periodic benefit risk evaluation report (PBRER)

The main objective of a PBRER is to present a comprehensive, concise and critical analysis of the risk-benefit balance of the pharmaceutical product taking into account new or emerging information in the

Context of cumulative information on risks and benefits. The PBRER is therefore a tool for post-authorization evaluation at defined time points in the lifecycle of a product.

For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorization phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorization clinical trials. A different risk-benefit balance may emerge as pharmacovigilance reveals further information about safety. The marketing authorization holder shall therefore reevaluate the risk-benefit balance of its own pharmaceutical products in populations exposed. This structured evaluation shall be undertaken in the context of ongoing pharmacovigilance and risk management to facilitate optimization of the risk-benefit balance through effective risk minimization.

Urgent safety information shall be reported through the appropriate mechanism. A PBRER is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide the means by which new safety issues are detected. It is acknowledged that the review of the data in the PBRER may lead to new safety issues being identified.

7.2.2. Principles for the evaluation of the risk-benefit balance within PBRERs and scope of the information to be included

Benefit-risk evaluation shall be carried out throughout the lifecycle of the pharmaceutical product to promote and protect public health and to enhance patient safety through effective risk minimization.

After a marketing authorization is granted, it is necessary to continue evaluating the benefits and risks of pharmaceutical products in actual use and/or long term use, to confirm that the risk-benefit balance remains favorable.

The analysis of the risk-benefit balance shall incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available, with reasonable and appropriate effort, during the reporting interval for the pharmaceutical product in the context of what was known previously.

The risk evaluation shall be based on **all uses** of the pharmaceutical product. The scope includes evaluation of safety in real medical practice including use in **unauthorized indications** and **use which is not in line with the product information**. If use of the pharmaceutical product is identified where there are critical gaps in knowledge for **specific safety issues or populations**, such use shall be reported in the PBRER (e.g. use in pediatric population or in pregnant women). Sources of information on use outside authorization may include drug utilization data, information from spontaneous reports and publications in the literature.

The scope of the benefit information shall include both clinical trial and real world data in authorized indications.

The integrated benefit-risk evaluation shall be performed for all authorized indications and shall incorporate the evaluation of risks in all use of the pharmaceutical product (including use in unauthorized indications).

The evaluation shall involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.
2. Critically summarizing relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the pharmaceutical product.
3. Conducting an integrated benefit-risk analysis for all authorized indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorization for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorization holder does not have access to data from the clinical development period, the earliest possible applicable date shall be used as starting point for the inclusion and evaluation of the cumulative information.
4. Summarizing any risk minimization actions that may have been taken or implemented during the reporting interval, as well as risk minimization actions that are planned to be implemented.
5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

7.2.3. Principles for the preparation of PBRERs

Unless otherwise specified the marketing authorization holder shall prepare a single PBRER for all its pharmaceutical products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PBRER and any safety concerns shall be addressed accordingly. There might be exceptional scenarios where the preparation of separate

PBRERs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement shall be obtained from EDA.

Case narratives shall be provided in the relevant risk evaluation section of the PBRER where integral to the scientific analysis of a signal or safety concern. In this context, the term ―case narratives refer to clinical evaluations of individual cases rather than the CIOMS narratives. It shall not be necessary to provide the actual CIOMS narrative text included in the individual case safety report (ICSR) but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal.

When data received at the marketing authorization holder from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorization holder's product information, these data shall be included and discussed in the PBRER.

Each PBRER shall include interval as well as cumulative data. As the PBRER shall be a single stand–alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

7.2.4. Reference information

Risk minimization activities evaluated in the PBRER include updates to the product information. The reference product information for the PBRER shall include "core safety" and "authorized indications" components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PBRER, the reference product information document shall list all authorized indications in ICH countries or regions. When there are additional locally authorized indications, these indications may be either added to the reference product information or handled in the national appendix as considered most appropriate by the marketing authorization holder. The basis for the benefit evaluation shall be the baseline important efficacy and effectiveness information summarized in the PBRER section 17.1 ("Important baseline efficacy and effectiveness information").

Information related to a specific indication, formulation or route of administration shall be clearly identified in the reference product information.

The following possible options can be considered by the marketing authorization holders when selecting the most appropriate reference product information for a PBRER:

- Company core data sheet (CCDS)
  - It is common practice for marketing authorization holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PBRER is for each marketing authorization holder to use the CCDS in effect

at the end of the reporting interval, as reference product information for both the risk sections of the PBRER as well as the main authorized indications for which benefit is evaluated.

- When the CCDS does not contain information on authorized indications, the marketing authorization holder shall clearly specify which document is used as reference information for the authorized indications in the PBRER.

- Other options for the reference product information
  - When no CCDS or CCSI exist for a product (e.g. where the product is authorized in only one country or region, or for /generics), the marketing authorization holder shall clearly specify the reference information being used. This may comprise Egyptian product information.
  - Where the reference information for the authorized indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval shall be included as an appendix to the PBRER.

The marketing authorization holder shall continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PBRER section 4 (“Changes to the reference safety information‖”) and where relevant, discussed in PBRER section 16 (“Signal and risk evaluation‖”). These changes may include:

- Changes to contraindications, warnings/precautions sections;
- Addition to adverse reactions and interactions;
- Addition of important new information on use in overdose; and
- Removal of an indication or other restrictions for safety or lack of efficacy reasons.

The marketing authorization holder shall provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PBRER) as an appendix to the PBRER. The reference product information shall be dated and version controlled. Where new information on safety that could warrant changes to the authorized product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PBRER, this information shall be included in the PBRER section 14 (“Late-breaking information”), if feasible.

The marketing authorization holder shall provide, in the national appendix, information on any final, ongoing and proposed changes to the national or local authorized product information.

7.2.5. Format and contents of the PBRER

The PBRER shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last PBRER. Cumulative information shall be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment. Because clinical development of a pharmaceutical product frequently continues following marketing authorization, relevant information from post-authorization studies or clinical trials in unauthorized indications or populations shall also be included in the PBRER. Similarly, as knowledge of the safety of a pharmaceutical product may be derived from evaluation of other data associated with off-label use, such knowledge shall be reflected in the risk evaluation where relevant and appropriate.

The PBRER shall provide summaries of data relevant to the benefits and risks of the pharmaceutical product, including results of all studies with a consideration of their potential impact on the marketing authorization.

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PBRERs include the following:

- Non-clinical studies;
- Spontaneous reports (e.g. on the marketing authorization holder's safety database);
- Active surveillance systems (e.g. sentinel sites);
- Investigations of product quality;
- Product usage data and drug utilization information;
- Clinical trials, including research in unauthorized indications or populations;
- Observational studies, including registries;
- Patient support programs;
- Systematic reviews and meta-analysis;
- Marketing authorization holders sponsored websites5;
- Published scientific literature or reports from abstracts, including information presented at scientific meetings;
- Unpublished manuscripts;
- Licensing partners, other sponsors or academic institutions and research networks;
- Competent authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorization holder to present safety, efficacy and effectiveness information in the PBRER and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the marketing authorization holder, a list of the sources of information used to prepare the PBRER can be provided as an appendix to the PBRER.

When preparing the PBRER, the ICH-E2C(R2) guideline on PBRER shall be applied. Guidance on the titles, order and content of the PBRER sections is provided in below, when no relevant information is available for any of the sections, this shall be stated.

- Part I: Title page including signature
- Part II: Executive Summary
- Part III: Table of Contents

1. Introduction
2. Worldwide marketing authorization status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns

5.1.Cumulative subject exposure in clinical trials

5.2. Cumulative and interval patient exposure from marketing experience

6. Data in summary tabulations

6.1.Reference information

6.2.Cumulative summary tabulations of serious adverse events from clinical trials
6.3.Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
7.1. Completed clinical trials
7.2. Ongoing clinical trials
7.3. Long-term follow-up
7.4. Other therapeutic use of pharmaceutical product
7.5. New safety data related to fixed combination therapies
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
9.1. Other clinical trials
9.2. Medication errors
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, ongoing or closed
16. Signal and risk evaluation
16.1. Summaries of safety concerns
16.2. Signal evaluation
16.3. Evaluation of risks and new information
16.4. Characterization of risks
16.5. Effectiveness of risk minimization (if applicable)
17. Benefit evaluation
17.1. Important baseline efficacy and effectiveness information
17.2. Newly identified information on efficacy and effectiveness
17.3. Characterization of benefits
18. Integrated benefit-risk analysis for authorized indications
18.1. Benefit-risk context – Medical need and important alternatives
18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the PBRER

7.2.5.1.PBRER title page

The title page shall include the name of the pharmaceutical product(s) and substance, international birth date (IBD) (the date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world), reporting interval, date of the report, marketing authorization holder details and statement of confidentiality of the information included in the PBRER.

The title page shall also contain the signature.

7.2.5.2.PBRER executive summary

An executive summary shall be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PBRER and shall contain the following information:

- Introduction and reporting interval;
- Pharmaceutical product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
- Estimated cumulative clinical trials exposure;
- Estimated interval and cumulative exposure from marketing experience;
- Number of countries in which the pharmaceutical product is authorized;
- Summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk
- analysis evaluation” of the PBRER);
- Actions taken and proposed for safety reasons, (e.g. significant changes to the reference product information, or other risk minimization activities);
- Conclusions.

7.2.5.3.PBRER table of contents

The executive summary shall be followed by the table of contents.

PBRER section “Introduction”

The marketing authorization holder shall briefly introduce the product(s) so that the PBRER “stands alone” but it is also placed in perspective relative to previous PBRERs and circumstances. The introduction shall contain the following information:

- IBD, and reporting interval;
- Pharmaceutical product(s), therapeutic class(es), mechanism(s) of action, authorized indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
- A brief description of the population(s) being treated and studied;

PBRER section “Worldwide marketing authorization status"

This section of the PBRER shall contain a brief narrative overview including: date of the first authorization worldwide, indications(s), authorized dose(s), and where authorized.

PBRER section “Actions taken in the reporting interval for safety reasons”

This section of the PBRER shall include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the marketing authorization holder, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- A significant influence on the risk-benefit balance of the authorized pharmaceutical product; and/or an
- Impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

If known, the reason for each action shall be provided and any additional relevant information shall be included as appropriate. Relevant updates to previous actions shall also be summarised in this section.

Examples of significant actions taken for safety reasons include:

Actions related to investigational uses:

- Refusal to authorize a clinical trial for ethical or safety reasons;
- Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- Recall of investigational drug or comparator;
- Failure to obtain marketing authorization for a tested indication including voluntary withdrawal
- Marketing authorization application;
- Risk management activities, including: Protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in Study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
  - Restrictions in study population or indications;
  - Changes to the informed consent document relating to safety concerns;
  - Formulation changes;
  - Addition by regulators of a special safety-related reporting requirement;
  - Issuance of a communication to investigators or healthcare professionals; and
  - Plans for new studies to address safety concerns.

Actions related to marketing experience:

- Failure to obtain or apply for a marketing authorization renewal;
- Withdrawal or suspension of a marketing authorization;
- Actions taken due to product defects and quality issues;
- Suspension of supply by the marketing authorization holder;
- Risk management activities including:
  - Significant restrictions on distribution or introduction of other risk minimization measures;
  - Significant safety-related changes in labeling documents including restrictions on use or population treated;
  - Communications to health care professionals; and
  - New post-marketing study requirement(s) imposed by competent authorities.

<u>PBRER section “Changes to reference safety information”</u>

This PBRER section shall list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes shall be provided in the appropriate sections of the PBRER.

PBRER section "Estimated exposure and use patterns"

PBRERs shall provide an accurate estimate of the population exposed to the pharmaceutical product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorization holder, including the results of observational or drug utilization studies.

This PBRER section shall provide estimates of the size and nature of the population exposed to the pharmaceutical product including a brief description of the method(s) used to estimate the subject/patient exposure and the limitations of that method.

Consistent methods for calculating subject/patient exposure shall be used across PBRERs for the same pharmaceutical product. If a change in the method is appropriate, both methods and calculations shall be provided in the PBRER introducing the change and any important difference between the results using the two methods shall be highlighted.

PBRER sub-section "Cumulative subject exposure in clinical trials"

This section of the PBRER shall contain the following information on the patients studied in clinical trials sponsored by the marketing authorization holder, if applicable presented in tabular formats:

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational pharmaceutical product, placebo, and/or active comparator(s) since the DIBD. It is recognized that for "old products", detailed data might not be available;
- More detailed cumulative subject exposure in clinical trials shall be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development program);
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
- If clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data shall be provided as appropriate;
- When there are substantial differences in time of exposure between subjects randomised to the investigational pharmaceutical product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or - years);
- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;
- If the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure shall also be presented by indication, where available;
- For individual trials of particular importance, demographic characteristics shall be provided separately.

PBRER sub-section "Cumulative and interval patient exposure from marketing experience"

Separate estimates shall be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PBRER). Although it is recognized that it is often difficult to obtain and validate exposure data, the number of patients exposed shall be provided whenever possible, along with the method(s) used to determine the estimate. Justification shall be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, shall be presented along with the method(s) used to derive them.

Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data shall be presented according to the following categories:

1. Post-authorization (non-clinical trial) exposure:
   An overall estimation of patient exposure shall be provided. In addition, the data shall be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups shall be presented, if possible.
   For locally produced products that are marketed outside Egypt, the MAH shall include the estimate exposure in all the countries where the product is marketed.
2. Post-authorization use in special populations:
   Where post-authorization use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation shall be provided. Sources of such data may include for instance non-interventional studies designed to obtain this information, including registries. Other sources of information may include data collection outside a study environment including information collected through spontaneous reporting systems (e.g. information on reports of pregnancy exposure without an associated adverse event may be summarized in this section). Populations to be considered for discussion include, but might not be limited to:
   - Pediatric population;
   - Elderly population;
   - Pregnant or lactating women;
   - Patients with hepatic and/or renal impairment;
   - Patients with other relevant co-morbidity;
   - Patients with disease severity different from that studied in clinical trials;
   - Sub-populations carrying relevant genetic polymorphism(s);
   - Populations with specific racial and/or ethnic origins.
3. Other post-authorization use:
   If the marketing authorization holder becomes aware of a pattern of use of the pharmaceutical product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an antiepileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without reference to adverse reactions shall be summarized in this section as

applicable. Such information may be received via spontaneous reporting systems, medical information queries, customer's complaints, screening of digital media or via other information sources available to the marketing authorization holder. If quantitative information on use is available, it shall be provided.
If known, the marketing authorization holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information may be linked to clinical guidelines, clinical trial evidence, or an absence of authorized alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorization holder shall use the appropriate sections of the reference product information that was in effect at the end of

the reporting interval of the PBRER (e.g. authorized indication, route of administration, contraindications).
Signals or risks identified from any data or information source shall be presented and evaluated in the relevant sections of the PBRER.

PBRER section "Data in summary tabulations"
The objective of this PBRER section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the marketing authorization holder graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) shall be presented in the summary tabulations.

The seriousness of the adverse events/reactions in the summary tabulations shall correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICHE2A9. When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction shall be reflected in the summary tabulations. Seriousness shall not be changed specifically for the preparation of the PBRERs.

PBRER sub-section "Reference information"
This sub-section of the PBRER shall specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

PBRER sub-section "Cumulative summary tabulations of serious adverse events from clinical trials"
This PBRER sub-section shall provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorization holder's clinical trials, from the DIBD to the data lock point of the current PBRER. The marketing authorization holder shall explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) shall be organized by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the

comparator arm(s) (active comparators, placebo) used in the clinical development program. Data can be integrated across the program. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables. This sub-section shall not serve to provide analyses or conclusions based on the serious adverse events.
The following points shall be considered:

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations shall include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.
- In general, the tabulation(s) of serious adverse events from clinical trials shall include only those terms that were used in defining the case as serious and non-serious events shall be included in the study reports.
- The tabulations shall include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and marketing authorization holders shall not unblind data for the specific purpose of preparing the PBRER.
- Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions shall be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

PBRER sub-section “Cumulative and interval summary tabulations from post-marketing data sources”

This sub-section of the PBRER shall provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PBRER. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources shall be presented in a single table, with interval and cumulative data presented side-by-side. The table shall be organized by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.

For marketed pharmaceutical products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and shall be considered to be suspected adverse reactions for regulatory reporting purposes.

For locally produced products that are marketed outside Egypt, the MAH shall collect and collate reports from those countries where the product is marketed in, to be reflected under this section.

Analysis or conclusions based on the summary tabulations shall not be provided in this PBRER subsection.

PBRER section "Summaries of significant findings from clinical trials during the reporting interval"

This PBRER section shall provide a summary of the clinically important emerging efficacy and safety findings obtained from the marketing authorization holder's sponsored clinical trials during the reporting interval, from the sources specified in the sub-sections listed below. When possible and relevant, data categorized by sex and age (particularly pediatrics versus adults), indication, dose, and region shall be presented.

Signals arising from clinical trial sources shall be tabulated in PBRER section 15 ("Overview on signals: new, ongoing or closed").

Evaluation of the signals, whether or not categorized as refuted signals or either potential or identified risk, that were closed during the reporting interval shall be presented in PBRER section 16.2 ("Signal evaluation").

New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal shall be evaluated and characterized in PBRER sections 16.3 ("Evaluation of risks and new information") and 16.4 ("Characterization of risks") respectively.

Findings from clinical trials not sponsored by the marketing authorization holder shall be described in the relevant sections of the PBRER.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in authorized indications shall also be summarized in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness shall be summarized in section 13 ("Lack of efficacy in controlled clinical trials").

Information from other clinical trials/study sources shall be included in the PBRER sub-section 9.1 ("Other clinical trials").

In addition, the marketing authorization holder shall include an appendix listing the sponsored post-authorization interventional trials with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the pharmaceutical product that were completed or ongoing during the reporting interval. The listing shall include the following information for each trial:

- Study ID (e.g. protocol number or other identifier);
- Study title (abbreviated study title, if applicable);
- Study type (e.g. randomized clinical trial, cohort study, case-control study);
- Population studied, including country and other relevant population descriptors (e.g. pediatric population or trial subjects with impaired renal function);
- Study start (as defined by the marketing authorization holder) and projected completion dates;

- Status: ongoing (clinical trial has begun) or completed (clinical study report is finalized).

PBRER sub-section "Completed clinical trials"
This sub-section of the PBRER shall provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

PBRER sub-section "Ongoing clinical trials"
If the marketing authorization holder is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this sub-section shall briefly summarize the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

PBRER sub-section "Long term follow-up"
Where applicable, this sub-section shall provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

PBRER sub-section "Other therapeutic use of pharmaceutical product"
This sub-section of the PBRER shall include clinically important safety information from other programs conducted by the marketing authorization holder that follow a specific protocol, with solicited reporting (e.g. expanded access programs, compassionate use programs, particular patient use, and other organized data collection).

PBRER sub-section "New safety data related to fixed combination therapies"
Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the active substance that is the subject of the PBRERs is also authorized or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section shall summarize important safety findings from use of the combination therapy.
- If the product itself is a fixed combination product, this PBRER sub-section shall summarize important safety information arising from the individual components whether authorized or under development.

The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.

<u>PBRER section "Findings from non-interventional studies"</u>

This section shall also summarize relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorization holder-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programs). This shall include relevant information from drug utilization studies when relevant to multiple regions

The marketing authorization holder shall include an appendix listing marketing authorization holder sponsored non-interventional studies conducted with the primary aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the pharmaceutical product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval.

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above shall also be included in the regional appendix of the PBRER.

Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PBRER. As for other information sources, the marketing authorization holder shall present signals or risks identified from such information in the relevant sections of the PBRER.

PBRER section "Information from other clinical trials and sources"

PBRER sub-section "Other clinical trials"
This PBRER sub-section shall summarize information relevant to the benefit-risk assessment of the pharmaceutical product from other clinical trial/study sources which are accessible by the marketing authorization holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

PBRER sub-section "Medication errors"
This sub-section shall summarize relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the pharmaceutical product. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

PBRER section "Non-clinical data"
This PBRER section shall summarize major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns shall be included in the PBRER, regardless of the outcome. Implications of these findings shall be discussed in the relevant evaluation sections of the PBRER.

PBRER section "Literature"

This PBRER section shall include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorization holder became aware of during the reporting interval, when relevant to the pharmaceutical product.

Literature searches for PBRERs shall be wider than those for individual adverse reaction cases as they shall also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

- The special types of safety information that shall be included, but which may not be found by a search constructed specifically to identify individual cases, include:
- Pregnancy outcomes (including termination) with no adverse outcomes;
- Use in pediatric populations;
- Compassionate supply, named patient use;
- Lack of efficacy;
- Asymptomatic overdose, abuse or misuse;
- Medication error where no adverse events occurred;
- Important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class shall be considered.

The publication reference shall be provided in the style of the Vancouver Convention.

PBRER section "Other periodic reports"

This PBRER section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PBRERs are prepared in agreement with EDA. In general, the marketing authorization holder shall prepare a single PBRER for a single active substance; however, if multiple PBRERs are prepared for a single pharmaceutical product, this section shall also summarize significant findings from other PBRERs if they are not presented elsewhere within the report. When available, based on the contractual agreements, the marketing authorization holder shall summarize significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, other marketing authorization holders or other contractual partners).

PBRER section "Lack of efficacy in controlled clinical trials"

This section shall summarize data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening

PBRER section "Late-breaking information"

The marketing authorization holder shall summarize in this PBRER section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PBRER. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the marketing authorization holder, a data monitoring committee, or a competent authority (worldwide) has taken for safety reasons. New individual case reports shall not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g. a well-documented case of aplastic anemia in a pharmaceutical product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, shall also be included in this section of the PBRER, where feasible.

The data presented in this section shall also be taken into account in the evaluation of risks and new information.

PBRER section "Overview of signals: new, ongoing, or closed"

The purpose of this section is to provide a high level overview of signals that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PBRER, a signal shall be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorization holder. It shall be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicine/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide).

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data, which is presented in section 16 ("Signal and risk evaluation") of the PBRER.

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PBRER, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognized risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PBRER.

Examples of new signals would therefore include new information on a previously:

- Close and refuted signal, which would result in the signal being re-opened.

- Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or Neutropenia is an identified risk and a well-documented case report of agranulocytosis with no presence of possible alternative causes is received).
- Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimization activities.

Within this section or as an appendix the marketing authorization holder shall provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation shall include the following information:

- A brief description of the signal;
- Date when the marketing authorization holder became aware of the signal;
- Status of the signal at the end of the reporting interval (close or ongoing);
- Date when the signal was closed, if applicable;
- Source of the signal;
- A brief summary of the key data;
- Plans for further evaluation; and
- Actions taken or planned.

The detailed signal assessments for closed signals are not to be included in this section but instead shall be presented in sub-section 16.2 (“Signal evaluation”) of the PBRER.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal shall be provided in PBRER sub-section 16.3 (“Evaluation of risks and new information”).

When a competent authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in a PBRER, the marketing authorization holder shall summarize the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it shall be included in the signal tabulation and discussed in sub-section 16.2 (“Signal evaluation”).

PBRER section “Signal and risk evaluation”

The purpose of this section of the PBRER is to provide:

- A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report.
- An evaluation of all signals closed during the reporting interval.
- An evaluation of new information with respect to previously recognized identified and potential risks.
- An updated characterization of important potential and identified risks, where applicable.

- A summary of the effectiveness of risk minimization activities in any country or region which may have utility in other countries or regions.

These evaluation sub-sections shall not summarize or duplicate information presented in previous sections of the PBRER but shall rather provide interpretation and critical appraisal of the information with a view towards characterizing the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PBRER but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) shall be provided.

PBRER sub-section "Summary of safety concerns"
The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PBRER. It shall provide the following safety information:

- Important identified risks;
- Important potential risks; and
- Missing information.

PBRER sub-section "Signal evaluation"
This sub-section of the PBRER shall summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this sub-section are:

1. Those signals that, following evaluation, have been refuted as "false" signals based on medical judgement and scientific evaluation of the currently available information.
2. Those signals that, following evaluation, have been categorized as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation shall be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the marketing authorization holder.

It is recommended that the level of detail provided in the description of the signal evaluation shall reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals.
- Closed signals that are categorized as important potential risks.

- Closed signals that are categorized as important identified risks.
- Closed signals that are potential risks not categorized as important.
- Closed signals that are identified risks not categorized as important.

Where applicable the evaluations of closed signals can be presented by indication or population.

The description(s) of the signal evaluations can be included in this sub-section of the PBRER or in an appendix. Each evaluation shall include the following information as appropriate:

- Source or trigger of the signal;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardized MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
- Results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
- Discussion;
- Conclusion.

Marketing authorization holder's evaluations and conclusions for refuted signals shall be supported by data and clearly presented.

PBRER sub-section "Evaluation of risks and new information"
This sub-section shall provide a critical appraisal of new information relevant to previously recognized risks that is not already included in sub-section 16.2 ("Signal evaluation"). New information that constitutes a signal with respect to a previously recognized risk or previously refuted signal shall be presented in the signals tabulation and evaluated in subsection 16.2 ("Signal evaluation"), if the signal is also closed during the reporting interval of the PBRER.

Updated information on a previously recognized risk that does not constitute a signal shall be included in this sub-section. Examples include information that confirms a potential risk as an identified risk, or information which allows any other further characterization of a previously recognized risk.

New information can be organized as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorized as important.
4. New information on other identified risks not categorized as important.
5. Update on missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PBRER. This shall be concise and interpret the impact, if any, on the understanding and characterization of the risk. Where applicable, the evaluation will form the basis for an updated characterization of important potential and identified risks in sub-section 16.4 ("Characterization

of risks") of the report. It is recommended that the level of detail of the evaluation included in this subsection shall be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of the new information and missing information update(s) can be included in this sub-section of the PBRER, or in an appendix. Each evaluation shall include the following information as appropriate:

- Source of the new information;
- Background relevant to the evaluation;
- Method of evaluation, including data sources, search criteria, and analytical approaches;
- Results – a summary and critical analysis of the data considered in the risk evaluation;
- Discussion;
- Conclusion, including whether or not the evaluation supports an update of the characterization of any of the important potential and identified risks in sub-section 16.4 ("Characterization of risks")

Any new information on populations exposed or data generated to address previously missing information shall be critically assessed in this sub-section. Unresolved concerns and uncertainties shall be acknowledged.

PBRER sub-section "Characterization of risks"
This sub-section shall characterize important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information.

Depending on the nature of the data source, the characterization of risk may include, where applicable:

- Frequency;
- Numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
- Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- Estimate of relative risk and precision of estimate;
- Estimate of absolute risk and precision of estimate;
- Impact on the individual patient (effects on symptoms, quality or quantity of life);
- Public health impact;
- Patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- Dose, route of administration;
- Duration of treatment, risk period;
- Preventability (i.e. predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- Reversibility;
- Potential mechanism; and strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it shall be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) shall be discussed.

For PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- Risks relating to the active substance;
- Risks related to a specific formulation or route of administration (including occupational exposure);
- Risks relating to a specific population; and
- Risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

PBRER sub-section: "Effectiveness of risk minimization (if applicable)"
Risk minimization activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a pharmaceutical product or to reduce its severity shall it occur. The aim of a risk minimization activity is to reduce the probability or severity of an adverse drug reaction. Risk minimization activities may consist of routine risk minimization (e.g. product labeling) or additional risk minimization activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PBRER shall contain the results of assessments of the effectiveness of risk minimization activities relevant to the risk-benefit assessment.

Relevant information on the effectiveness and/or limitations of specific risk minimization activities for important identified risks that has become available during the reporting interval shall be summarized in this sub-section of the PBRER.

Insights into the effectiveness of risk minimization activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarized by region, if applicable and relevant.

To evaluate the effectiveness of additional risk minimization measures two categories of indicators shall be considered:

- Process indicators
- Outcome indicators

Process indicators are necessary to gather evidence that the implementing steps of additional risk minimization measures have been successful. These process indicators shall provide insight into what extent the program has been executed as planned and whether the intended impacts on behavior have been observed. Implementation metrics shall be identified in advance and tracked over time. The knowledge gained may be used to support corrective implementation action as needed. Assessing the implementation process can also improve understanding of the process(es)

and causal mechanism(s) whereby the additional risk minimization measure(s) did or did not lead, to the desired control of specified important risks.

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

In rare circumstances when it is fully justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators

PBRER section "Benefit evaluation"

PBRER sub-sections 17.1 ("Important baseline efficacy and effectiveness information") and 17.2 ("Newly identified information on efficacy and effectiveness") Provide the baseline and newly identified benefit information that support the characterization of benefit described in *sub-section 17.3 ("Characterization of benefits")* that in turn supports the benefit-risk evaluation in section 18 ("Integrated benefit-risk analysis for authorized indications").

PBRER sub-section "Important baseline efficacy and effectiveness information" This sub-section of the PBRER summarizes information on both efficacy and effectiveness of the pharmaceutical product at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information shall relate to authorized indication(s) of the pharmaceutical product listed in the reference product information.
For pharmaceutical products with multiple indications, populations, and/or routes of administration, the benefit shall be characterized separately by these factors when relevant.

The level of detail provided in this sub-section shall be sufficient to support the characterization of benefit in the PBRER sub-section 17.3 ("Characterization of benefits") and the benefit-risk assessment in section 18 ("Integrated benefit-risk analysis for authorized indications").

PBRER sub-section "Newly identified information on efficacy and effectiveness"
For some products, additional information on efficacy or effectiveness in authorized indications may have become available during the reporting interval. Such information shall be presented in this subsection of the PBRER. For authorized indications, new information on efficacy and effectiveness under conditions of actual use shall also be described in this sub-section, if available. New information on efficacy and effectiveness in uses other than the authorized indications shall not be included unless relevant for the benefit-risk evaluation in the authorized indications.

Information on indications newly authorized during the reporting interval shall also be included in this sub-section.

The level of detail provided in this section shall be sufficient to support the characterization of benefit in sub-section 17.3 ("Characterization of benefits") and the benefit-risk assessment in section 18 ("Integrated benefit-risk analysis for authorized indications").

In this sub-section, particular attention shall be given to vaccines, anti-infective agents or other pharmaceutical products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

PBRER sub-section "Characterization of benefits"
This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications.

The level of detail provided in this sub-section shall be sufficient to support the analysis of benefit-risk in section 18 ("Integrated benefit-risk analysis for authorized indications").

When there are no new relevant benefit data, this sub-section shall provide a characterization of the information in sub-section 17.1 ("Important baseline efficacy and effectiveness information").

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this sub-section shall be succinct.

This sub-section shall provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:

- A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- New information that challenges the validity of a surrogate endpoint, if used;
- Clinical relevance of the effect size;
- Generalizability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
- Adequacy of characterization of dose-response;
- Duration of effect;
- Comparative efficacy; and

- A determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

<u>PBRER section "Integrated benefit-risk analysis for authorized indications"</u>
The marketing authorization holder shall provide in this PBRER section an overall appraisal of the benefit and risk of the pharmaceutical product as used in clinical practice. Whereas sub-sections 16.4

("Characterization of risks") and 17.3 ("Characterization of benefits") present the risks and benefits, this section shall provide a critical analysis and integration of the key information in the previous sections and shall not simply duplicate the benefit and risk characterization presented in the subsections mentioned above.

PBRER sub-section "Benefit-risk context - medical need and important alternatives"

This sub-section of the PBRER shall provide a brief description of the medical need for the pharmaceutical product in the authorized indications and summarized alternatives (medical, surgical or other; including no treatment).

PBRER sub-section "Benefit-risk analysis evaluation"

A risk-benefit balance is specific to an indication and population. Therefore, for products authorized for more than one indication, risk-benefit balances shall be evaluated and presented by each indication individually. If there are important differences in the risk-benefit balance among populations within an indication, the benefit-risk evaluation shall be presented by population, if possible.

The benefit-risk evaluation shall be presented and discussed in a way that facilitates the comparison of benefits and risks and shall take into account the following points:

- Whereas previous sections/sub-sections shall include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation shall be specified. The key information presented in

  the previous benefit and risk section/sub-sections shall be carried forward for integration in the benefit-risk evaluation.
- Consider the context of use of the pharmaceutical product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).
- With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorized indications or populations, off-label use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence shall be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment shall be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation shall be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods shall be included.

- Economic considerations (e.g. cost-effectiveness) shall not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PBRER has been requested, a detailed benefit-risk analysis shall be presented based on cumulative data. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

PBRER section "Conclusions and actions"

A PBRER shall conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorized indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorization holder shall assess the need for changes to the reference product information and propose changes as appropriate.

In addition, and as applicable, the conclusions shall include preliminary proposal(s) to optimize or further evaluate the risk-benefit balance for further discussion with EDA. This may include proposals for additional risk minimization activities.

For products with a pharmacovigilance or risk management plan, the proposals shall also be considered for incorporation into the pharmacovigilance plan and/or risk minimization plan, as appropriate.

Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorization holder shall draw conclusions in the PBRER as to the need for changes and/or actions, including implications for the approved summary of product characteristics (SmPC) for the product(s) for which the PBRER is submitted.

Proposed changes to the reference product information shall be described in this section of the PBRER.

The national appendix shall include proposals for product information (SmPC and package leaflet) together with information on ongoing changes when applicable.

Appendices to the PBRER

A PBRER shall contain the following appendices as appropriate, numbered as follows:

1. Reference information.
2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
3. Tabular summary of safety signals (if not included in the body of the report).
4. Listing of all the marketing authorization holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterizing, or quantifying a

safety hazard or confirming the safety profile of the pharmaceutical product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.

5. List of the sources of information used to prepare the PBRER (when desired by the marketing authorization holder).
6. EU appendix (in case of multinational companies)
7. National appendix including the following subsections:

a) Subsection "Current national product information"

- This subsection shall contain a clean copy of the national product information approved in Egypt and which is in effect at the end of the reporting interval, if not applicable, the approved stamped SmPC can be attached as a separate PDF.
- When meaningful differences exist between reference safety information (e.g., CCDS or CCSI) and the safety information in the national product information (national SmPC and package leaflet), a brief comment shall be prepared by the company, describing these local differences with track change version.
- The reference product information document shall list all authorized indications in ICH countries or regions. When there are additional locally authorized indications in Egypt, these indications may be either added to the reference product information or handled in the national appendix as considered most appropriate by the marketing authorization holder and EDA.

b) Subsection "Proposed product information"

The assessment of the need for amendments to the product information is incorporated within the PBRER assessment procedure. The regulatory opinion shall include recommendations for updates to product information where needed. Marketing authorization holders shall provide the necessary supportive documentation and references within the PBRER or in this appendix to facilitate this.

Within the PBRER, the marketing authorization holder is required to consider the impact of the data and evaluations presented within the report, on the marketing authorization. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorization holder shall draw conclusions in the PBRER as to the need for changes and/or actions, including implications for the approved SmPC(s) for the product(s) for which the PBRER is submitted.

In this sub-section, the marketing authorization holder shall provide the proposals for product information (SmPC and package leaflet) based on the above mentioned evaluation. These shall be based on all authorized indications in Egypt.

A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PBRER shall be provided.

All the SmPCs and packages leaflets covered by the PBRER and in effect at the data lock point, shall be reviewed to ensure that they reflect the appropriate information according to the cumulative data included and analyzed in the PBRER.

Amendments to the product information shall not be postponed or delayed until the PBRER submission and amendments not related to the information presented in the PBRER, shall not be proposed within the PBRER procedure. It is the obligation of the marketing authorization

holder to submit a variation in accordance with the national regulation on variations to the terms of a marketing authorization.
A brief description of ongoing procedures (e.g. variations) to update the product information shall be provided in this section.

c) *Subsection "Proposed additional pharmacovigilance and risk minimization activities"*
This sub-section shall include proposals for additional pharmacovigilance and additional risk minimization activities based on the conclusions and actions of the PBRER, including a statement of the intention to submit a RMP or an updated RMP when applicable.

d) *Subsection "Summary of ongoing safety concerns"*
In order to support the information provided in the PBRER section 16.1 ―Summary of safety concerns, Table ―Summary – Ongoing safety concerns shall be included in this PBRER sub-section. This table shall be extracted from the version of RMP available at the beginning of the PBRER reporting interval

e) *Subsection "Worldwide marketing authorization status table"*
In addition to PBRER section worldwide marketing authorization status, a cumulative table with the following information shall be provided for any indication, for all countries where a regulatory decision about marketing authorization has been made related to the following:

- Dates of first marketing authorization approval or date of application in case the entry is related to a refusal of marketing authorization application;
- Countries (worldwide) in which the pharmaceutical product was authorized
- Product trade name(s)
- Dosage form
- Treatment indications and special populations covered by the market authorization, when relevant.
- Current authorization status; authorized, withdrawn or suspended. In addition, explanation shall be provided in case of any type of lack of approval;
- Dates when the marketing authorization has been withdrawn or dates when the marketing authorization has been suspended either by a regulatory authority or voluntarily by the MAH;
- Current marketing status; marketed, not marketed or never launched. In addition, the date of such status shall be provided
- Withdrawal of an application for authorization or refusal of granting the authorization; explanation shall be provided

In case of Multinational and International companies, the National appendix shall also include the following subsections:
Sub-section "Patient exposure in the Egypt": This sub-section shall provide sales data and interval patient exposure in Egypt (for each year of the reporting interval separately if the PBRER covers more than 1 year).

Sub-section "Adverse drug reactions reporting in the Egypt": This sub-section shall provide summary tabulations in Egypt during the reporting interval (in a table organized by MedDRA SOC) and the number of cases reported in Egypt during the PBRER interval

Sub-section "Studies in the Egypt (if any)": This section shall list all studies (investigational or observational) in Egypt during the reporting interval and cumulatively, either planned, ongoing or completed.

7.3. Operation in Egypt

7.3.1. Routine submission of PBRERs

Taking into consideration the following about the PBRER:

- The main objective of a PBRER is to present a comprehensive, concise and critical analysis of the risk-benefit balance of the pharmaceutical product taking into account **all** new or emerging information (from **all countries** in which the product is authorized) in the context of cumulative information on risks and benefits;
- The required format and content of PBRERs in EU and in Egypt are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline.

Accordingly, the PBRER can be described as a **global pharmacovigilance document** (worldwide information and same format & content) hence, the same PBRER is submitted to several authorities worldwide.

As this guideline was based on the European Good Pharmacovigilance Practice; the "list of European Union reference dates"(EURD) is adopted in the context of this guideline. Hence the PBRERs submitted in Egypt shall follow the dates & frequency stated in the most updated version of the list; this does not undermine the right of EDA to request the submission of PBRERs at any time or to change as appropriate the submission frequency on the national level.

- For active substances and combinations of active substances **not included in the EURD list**, the MAH shall check the PBRER supplementary list published on EDA's website, which is updated every 3 months. Access here.
- For active substances/combinations **not included in both lists**, the MAH shall submit a proposal request to define frequency to the Pharmaceutical Vigilance General Administration.

In case of submitting PBRERs of not marketed products: Such information shall be supported by a statement signed on MAH official paper by the CEO (or the equivalent positions at multinational companies on a local level) declaring that your product is not launched yet, never been marketed or sold by any tenders along with adequate justification and that the company will inform us once the product is marketed.

7.3.2. List of European Union reference dates and frequency of submission of PBRERs

7.3.2.1. Objectives of the "EU reference dates list"

The European Medicines Agency (EMA) shall make public a list of Union reference dates (hereinafter referred to as list of EU reference dates or EURD list) and frequency of submission of PBRERs by means of the European medicines web-portal.

The objectives of the list of EU reference dates and frequency of submission of PBRERs are:

- Harmonization of DLP & frequency of submission of PBRERs for the same active substance and combination of active substance.
- Single EU assessment & reassessment of the risk-benefit balance of an active substance based on all available safety data.
- The periodicity is defined on a risk based approach in order to prioritize the periodic re-evaluation of the risk benefit balance of active substances in a way that best protects public health.

7.3.2.2. Description of the "EU reference dates list"

The list of EU reference dates and frequency of submission of PBRERs consists of a comprehensive list of substances and combinations of active substances- in alphabetical order- for which PBRERs shall be submitted in accordance with the EU reference date and the frequency as determined in the list. The list is updated in line with the list of all pharmaceutical products for human use authorized in the EU.
The EU reference dates list shall contain the following information:

- The EU reference dates;
- The frequencies of submission of PBRERs;
- The data lock points of the next submissions of PBRERs;
- The next submission date has been included to support MAHs' planning in terms of the PBRER submission and ensure that all relevant PBRERs are received prior to the start of the assessment procedure
- The date of publication (on the European Medicines web-portal) of the frequency for PBRERs submission and data lock point for each active substance and combination of active substances. Any change to the dates of submission and frequency on PBRERs specified in the marketing authorization shall take effect 6 months after the date of such publication.

Where specificity is deemed necessary, the list shall include the scope of the PBRER and related single assessment procedure such as:

- Whether or not it shall cover all the indications of the substance or combination of active substances;
- Whether or not it shall cover all the formulations/routes of administration of the products containing a substance or combination of active substances;

7.3.2.3. Criteria used for defining the frequency of submission of PBRERs

The following prioritization criteria shall be taken into account when defining the frequency of submission for a given active substance or combination of active substances:

- Information on risks or benefits that may have an impact on the public health;
- New product for which there is limited safety information available to date (includes pre- and post-authorization experiences);
- Significant changes to the product (e.g. new indication has been authorized, new pharmaceutical form or route of administration broadening the exposed patient population);

- Vulnerable patient populations/poorly studied patient populations, missing information (e.g. children, pregnant women) while these populations are likely to be exposed in the post authorization setting;
- Signal of/potential for misuse, medication error, risk of overdose or dependency;
- The size of the safety database and exposure to the pharmaceutical product;
- Pharmaceutical products subjected to additional monitoring.

Any change in the criteria listed above for a given active substance or combination of active substances may lead to an amendment of the list of EU reference dates (e.g. increase of the frequency for PBRER submission).

7.3.2.4. Maintenance of the list of EU reference dates

The maintenance of the list of EU reference dates shall facilitate regulatory responsiveness to public health concerns and therefore the list will be subject to changes to reflect the decisions taken

(e.g. following signal detection).

The information included in the list such as the active substances and combinations of active substances, the frequencies of submission of PBRERs and data lock points may need to be updated when considered necessary. Changes to the list may be applied on one of the following grounds:

- Emergence of new information that might have an impact on the risk-benefit balance of the active substances or combinations of active substances, and potentially on public health;
- Any change in the criteria used for the allocation of frequency for PBRER submission and defined above;
- Active substance newly authorized.

7.3.3. Submission of PBRERs for pharmaceutical products: General requirement

The data lock points included in the "list of EU references dates" enable the synchronization of PBRERs submission and permit the single assessment on the national level. These data lock points are fixed on a certain date of the month, and shall be used to determine the submission date of the PBRER.

Unless otherwise specified in the list of EU reference dates and frequency of submission, or agreed with EDA, as appropriate, a single PBRER shall be prepared for all pharmaceutical products containing the same active substance and authorized for one marketing authorization holder. The PBRER shall cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorized under different names.

Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen shall be presented in a separate section of the PBRER and any safety concerns shall be addressed accordingly.

The adoption of the list of EU reference dates for the submission of PBRERs in Egypt does not undermine the right of EDA to request the submission of PBRERs at any time or to change as appropriate the submission frequency on the national level.

7.3.3.1. Submission of PBRERs in case of active substances not included in the EURD list

For pharmaceutical products containing an active substance or a combination of active substances NOT included in the EU reference dates list, the MAH shall check the **PBRER supplementary list** published on EDA's website. For active substances/combinations **not included in both lists**, the MAH shall submit a proposal request to define frequency to the Pharmaceutical Vigilance General Administration.

7.3.3.2. Pharmaceutical products with conditioned PBRERs submission frequency in the marketing authorization

Authorized pharmaceutical product for which the frequency and dates of submission of PBRERs are laid down as a condition in its marketing authorization;

- If this conditioned marketing authorization is granted **BEFORE** the EURD list becomes into effect in Egypt, and, if the active substance or a combination of active substances of this product is included in the "EU reference dates list", then the MAH shall submit variation -as appropriate- to update the frequency as published in the EURD list.
- If this conditioned marketing authorization is granted **AFTER** the EURD list becomes into effect in Egypt, then the MAH shall follow the frequency laid down in the marketing authorization.

Afterward, any changes to the dates and frequencies of submission of PBRERs specified in the list take effect **six months** after the date of the publication.

7.3.3.3. Submission of PBRERs for generic, well-established use, traditional herbal and homeopathic pharmaceutical products

As a general rule, PBRERs for these kind of pharmaceutical products are required to be submitted in the Egypt (unless otherwise is announced by EDA).

The **multinational** marketing authorization holders for any of these kinds of pharmaceutical products which **sometimes** are exempted from submitting PBRERs routinely for these products in the European Union; shall be attentive to the national requirements in Egypt as this European exemption is NOT applied in Egypt (unless otherwise is announced by EDA).

If for any reason the PBRERs of some of these products are no longer required by EDA to be submitted routinely, it is expected that marketing authorization holders will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the risk-benefit balance or the product information.

7.3.3.4. Submission of PBRERs for fixed dose combination products

Unless otherwise specified in the "list of EU reference dates and frequency of submission", if the substance that is the subject of the PBRER is also authorized as a component of a fixed combination pharmaceutical product, the marketing authorization holder shall either submit a separate PBRER for the combination of active substances authorized for the same marketing authorization holder with cross-references to the single-substance PBRER(s), or provide the combination data within one of the single-substance PBRERs.

7.3.3.5. Submission of PBRERs on demand of the authority in Egypt (ad hoc request)

In addition to the routine PBRER submission, marketing authorization holders shall submit PBRERs immediately upon special request from EDA. When the timeline for submission has not been specified in the request, marketing authorization holders shall submit the PBRER within 90 calendar days of the data lock point.

7.3.3.6. Timelines for PBRER submission

Each marketing authorization holder shall be responsible for submitting PBRERs for its own products

to EDA in Egypt according to the following timelines:

- Within 70 calendar days of the data lock point (day 0) for PBRERs covering intervals up to 12 months (including intervals of exactly 12 months); and
- Within 90 calendar days of the data lock point (day 0) for PBRERs covering intervals in excess of 12 months;
- The timeline for the submission of ad hoc PBRERs requested by EDA will normally be specified in the request, otherwise the ad hoc PBRERs shall be submitted within 90 calendar days of the data lock point.

7.3.4. Process for PBRER Assessment in Egypt

7.3.4.1. PBRER assessment by Pharmaceutical Vigilance General Administration (PVGA) at EDA

It is the responsibility of EDA in Egypt where the products are authorized to evaluate the PBRERs for these pharmaceutical products to determine whether there are new risks or whether risks have changed

or whether there are changes to the risk-benefit balance of the pharmaceutical products. This assessment is conducted in accordance with the national regulations through the "PBRER single assessment‖ procedure which means the assessment of all PBRERs for pharmaceutical products containing the same active substance or the same combination of active substances whether or not held by the same marketing authorization holder and for which the frequency and dates of submission of PBRERs have been harmonized (refer to the list of EU reference dates which is adopted in Egypt).

At PBRER receipt, EDA shall perform a technical validation of the report to ensure that the PBRER application is in a suitable format.

Upon establishment of the list of all pharmaceutical products for human use authorized in it and in the context of the "PBRER single assessment" procedure, EDA shall ensure that all marketing authorization holder(s) of the given substance in their country have submitted PBRER(s), as required. In the event where a PBRER has not been submitted - which indeed considered a non-compliance of the MAH -

EDA shall contact the concerned marketing authorization holder(s). However, this will not preclude the start of the single assessment procedure for other PBRER(s) of the same active substance.

Data of individual cases from National Pharmacovigilance and Safety reports database may be retrieved to support the PBRER assessment.

During the assessment, additional listings of individual cases may be requested in the context of the PBRER assessment procedure for adverse reactions of special interest and shall be provided by the marketing authorization holder within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual case safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request shall generally be provided.

Following the assessment of PBRERs, EDA shall consider whether any action concerning the marketing authorization for the pharmaceutical products containing the concerned active substance or combination of active substances is necessary (e.g. add a new contraindication, a restriction of the indication or a reduction of the recommended dose, the need to conduct a post-authorization safety study, request an update of the RMP, review of safety issues and/or close monitoring of events of interest …etc). EDA shall vary, suspend or revoke the marketing authorization when applicable according to the appropriate procedure at national level.
Furthermore, marketing authorization holders are reminded of their obligation to keep their marketing authorization up to date.

Amendments to the SmPC, package leaflet and labelling as a result of the PBRER assessment shall be implemented through the appropriate variation.

When the proposals for the product information include new adverse reactions in section 4.8 (“Undesirable effects”) of the SmPC, or modifications in the description, frequency and severity of the existing reactions, marketing authorization holders shall provide in the relevant sections of the PBRER appropriate information to allow the adequate description and classification of the frequency of the adverse reactions. If other sections of the SmPC (e.g. SmPC section 4.4 “Special warnings and precautions for use”) are considered to be updated, clear proposals shall be provided for EDA to consider during the PBRER assessment. The proposals shall be included in the PBRER national appendix.

The outcome of the PBRER assessment shall incorporate the new safety warnings and key risk minimization recommendations, arising from the assessment of the data in the PBRER, to be included in the relevant sections of the product information.

The assessment results and conclusions of EDA shall be provided to the marketing authorization holder.

7.3.5. Quality systems for PBRERs at the level of marketing authorization holders

Marketing authorization holders shall have in place structures and processes for the preparation, quality control, review and submission of PBRERs including follow-up during and after their

assessment. These structures and processes shall be described by means of written policies and procedures in the marketing authorization holder's quality system.

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PBRERs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality system shall describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PBRERs. There shall be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PBRERs. In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation shall underpin processes and cross departmental input to PBRER preparation.

It is important for MAHs that have products marketed outside Egypt, to gather information and screen literature from national journals of those countries where their products are marketed in; in addition to, other internationally known journals.

The PBRER shall also contain the assessment of specific safety issues requested by EDA in accordance with agreed timelines and procedures. The marketing authorization holder

shall have mechanisms in place to ensure that the requests made by EDA during the time of their PBRER assessment are properly addressed.

The provision of the data included in the summary tabulations shall undergo source data verification against the marketing authorization holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed shall be properly documented.

An appropriate quality system shall be in place in order to avoid failure to comply with PBRER requirements such as:

- Non-submission: complete non-submission of PBRERs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with EDA);
- Unjustified omission of information required;
- Poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardized medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;
- Submission of a PBRER where previous requests from EDA have not been addressed;
- Failure to provide an explicit evaluation of the risk-benefit balance of the pharmaceutical product;
- Failure to provide adequate proposals for the local authorized product information.

Any significant deviation from the procedures relating to the preparation or submission of PBRERs shall be documented and the appropriate corrective and preventive action shall be taken. This documentation shall be available at all times.

When marketing authorization holders are involved in contractual arrangements (e.g. licensor-licensee), respective responsibilities for preparation and submission of the PBRER to EDA shall be clearly specified in the written agreement.

When the preparation of the PBRER is delegated to third parties, the marketing authorization holder shall ensure that they are subject to a quality system compliant with the current legislation.

Explicit procedures and detailed agreements shall exist between the marketing authorization holder and third parties. The agreements may specifically detail the options to audit the PBRER preparation process.

7.3.5.1. Training of staff members related to the PBRER process

For all organizations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PBRERs are adequately qualified, experienced and trained according to the applicable guidelines. When appropriate, specific training for the different processes, tasks and responsibilities relating to the PBRER shall be in place. Training to update knowledge and skills shall also take place as necessary. Training shall cover legislation, guidelines, scientific evaluation and written procedures related to the PBRER process. Training records shall demonstrate that the relevant training was delivered prior to performing PBRER-related activities.

7.3.6. Quality systems and record management systems for PBRERs in the Egypt

7.3.6.1. Quality systems and record management systems at the level of the marketing authorization holder

Specific quality system procedures and processes shall be in place in order to ensure the update of product information by the marketing authorization holder in the light of scientific knowledge, including the assessments and recommendations.

It is the responsibility of the marketing authorization holder to check regularly the list of EU reference dates and frequency of submission (adopted by Egypt) published on the official website of EMA website and check regularly the PBRER supplementary list published on the official website of EDA to ensure compliance with the PBRER reporting requirements for their pharmaceutical products.

Systems shall be in place to schedule the production of PBRERs according to:

- The list of EU reference dates and frequency of PBRERs submission; or
- The conditions laid down in the national marketing authorization; or
- As defined by EDA as applicable (without any conditions in their marketing authorization or not included in the list of EU references dates and frequency of submission; or
- Ad hoc requests for PBRERs by EDA.

For those pharmaceutical products where the submission of an RMP is not required, the marketing authorization holder shall maintain on file a specification of important identified risks, important potential risks and missing information in order to support the preparation of the PBRERs.

The marketing authorization holder shall have procedures in place to follow the requirements established by EDA concerned for the submission of PBRERs.

The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system and therefore shall ensure that the pharmacovigilance system in place enables the compliance with the requirements established for the production and submission of PBRERs. In relation to the pharmaceutical products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV in relation to PBRERs shall include:

- Ensuring the necessary quality, including the correctness and completeness, of the data submitted in the PBRERs;
- Ensuring full response according to the timelines and within the procedure agreed (e.g. next PBRER) to any request from EDA concerned related to PBRERs;
- Awareness of the PBRER and assessment report conclusions and the decisions of EDA in order to ensure that appropriate action takes place.

The record retention times for product-related documents in the Pharmacovigilance systems and their quality systems chapter also apply to PBRERs and source documents related to the creation of PBRERs, including documents related to actions taken for safety reasons, clinical trials and post-authorization studies, relevant benefit information and documents utilized for the calculation of patient exposure.

7.3.6.2. Quality systems and record management systems at the level of EDA

EDA shall have in place a pharmacovigilance system for the surveillance of pharmaceutical products and for receipt and evaluation of all pharmacovigilance data including PBRERs. For the purpose of operating its tasks relating to PBRERs in addition to the pharmacovigilance system EDA shall implement a quality system (See Pharmacovigilance systems and their quality systems chapter).

EDA shall monitor marketing authorization holders for compliance with regulatory obligations for PBRERs. Additionally, EDA shall take in cases of non-compliance the appropriate regulatory actions as required (e.g. variation, suspension or revocation…etc.). EDA may exchange information in case of MAH non-compliance.

Where MAH's tasks related to PBRER procedures are delegated to third parties, EDA shall ensure that they are subject to a quality system in compliance with the obligations provided by the national regulation/legislation.

EDA shall have in place a process to technically validate the completeness of PBRER submissions.

Data from the National Pharmacovigilance and Safety reports database (e.g. line listings and summary tabulations) shall be retrieved and utilized as appropriate to support the PBRER assessment.

Written procedures shall reflect the different steps to follow for the maintenance and publishing of the list of dates and frequency of submission of PBRERs.

The record retention times for product-related documents in Pharmacovigilance systems and their quality systems chapter also apply to PBRER- system related documents (e.g. standard operating

procedures) and PBRER -related documents (e.g. PBRERs, assessment reports, the data retrieved from the National Pharmacovigilance and Safety reports database or other data used to support the PBRER assessment).

Addendum to clinical overview (ACO)

A critical discussion addressing the current benefit/risk balance for the product on the basis of a consolidated version of safety/efficacy data accumulated since the initial MAA or the last renewal, taking into account Periodic Safety Update Reports (PBRERs) submitted, suspected adverse reactions reports, additional pharmacovigilance activities and the effectiveness of risk minimization measures contained in the RMP, if applicable. In addition, it shall make reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience, new treatments available, which may change the outcome of the benefit/risk evaluation at the time of the original authorization or last renewal.

The information shall include both positive and negative results of clinical trials and other studies in all indications and populations, whether or not included in the marketing authorization, as well as data on the use of the pharmaceutical product where such use is outside the terms of the marketing authorization.

This Addendum shall be signed and accompanied by the CV of the expert. The clinical expert shall have the necessary technical or professional qualifications and may, but shall not necessarily, be the same qualified person responsible for pharmacovigilance.

The Addendum to the Clinical Overview shall contain the following information:

- Section titled “History of pharmacovigilance system inspections” (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) and an analysis of the impact of the findings overall on the benefit/risk balance of the pharmaceutical product.
- Section titled “Worldwide marketing authorization status” overview of number of countries where the product has been approved and marketed worldwide and the dates of approval and launching & clarify the marketing status in Egypt.
- Section titled “Actions taken for safety reasons (worldwide)” during the period covered since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission: description of significant actions related to safety that had a potential influence on the benefit-risk balance of the approved pharmaceutical product (e.g. suspension, withdrawal, temporary halt or premature ending of clinical trial for safety reasons, issue requiring communication to healthcare professionals,…)
- Section titled "Significant changes made to the Reference Information (RI)" shall address the significant changes made to the Reference Information (RI) for your own product during the period covered since the initial marketing authorization or since the last renewal. A track changes version of the document identifying the changes made during the period covered since

the initial marketing authorization or since the last renewal shall also be provided until 90 days prior to renewal submission.

- Section titled “Meaningful differences between Reference safety information (RI)” clarifying differences between Reference safety information (RI) (e.g.: current SmPC) & proposed SmPCs preferably in a tabulated form.
- Section titled "Estimated Exposure and Use patterns", data on cumulative exposure of subjects in clinical trials as well as of patients from marketing exposure. If the marketing authorization holder becomes aware of a pattern of use of the pharmaceutical product considered relevant for the implementation of the safety data, a brief description shall be provided; such patterns may include in particular off-label use
    - sub-section “Cumulative and interval patient exposure from marketing experience” shall include an estimate patient exposure, an estimate of the number of patients exposed shall be provided along with the method used to derive the estimate & clarify **Sales data and interval patient exposure in Egypt (for each year of the reporting interval separately)**.

      As guidance use the following equations:

      - Patient treatment years =Patient treatment days /365.25
      - Patient treatment days = no. of mg sold / No of mg per day (defined daily dose)
- Section titled “Data in summary tabulations” shall include the Summary tabulations of serious adverse events from clinical trials (if applicable) as well as summary tabulations of adverse reactions from post-marketing data sources reported during the period covered since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission and **data in Egypt during the reporting interval (in a table organized by MedDRA SOC) & the number of cases reported in Egypt during the ACO interval shall be clarified.**

MAHs shall enhancing the pharmacovigilance system and providing adequate training of company staff and adopting internal company regulation to mandate collection and reporting of safety data information are required.

In addition, following the below measures will help with the collection of cases:

- Build awareness for reporting among HCPs using MAH products.
- Enable efficient channels for reporting from HCPs and public.

- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies: description of any significant safety findings that had an impact on the conduct of clinical trials or non-interventional studies. It shall also address whether milestones from post-authorization safety studies, post-authorization efficacy studies, studies from the RMP pharmacovigilance plan and studies conducted as condition and obligations of the marketing authorization, have been reached in accordance with agreed timeframes.
- Section titled "Literature": adequately review of the published literature references during the period covered that had a potential impact on the benefit/risk of the pharmaceutical product & include summary of literature articles highlighting only the significant data along with the company’s comment on each Literature case. The full articles shall be annexed.
- Section titled "Risk evaluation": subsection titled "Characterization of risks": shall summaries any information related to important safety issues, evaluation and characterization of risks as well as effectiveness of risk minimizations for the period covered since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission".

- Section titled "Benefit evaluation" the MAH shall summarize important efficacy and effectiveness information (including information on lack of efficacy) for the period covered since the initial marketing authorization or since the last renewal until 90 days prior to renewal submission.
- Section titled "Benefit-risk balance" a discussion on the benefit-risk balance for the approved indication shall be presented, based on the above information.
- Section titled "Late-breaking information" shall summarize the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the addendum to the clinical overview.
- The Clinical expert statement shall be signed & accompanied by CV of the expert and shall:
  - Confirm that no new clinical data are available which change or result in a new risk-benefit evaluation.
  - Confirm that the product can be safely renewed at the end of a x-year period (check national regulations) for an unlimited period, or any action recommended or initiated shall be specified and justified.
  - Confirm that EDA has been kept informed of any additional data significant for the assessment of the benefit/risk ration of the product concerned.
  - Confirm that the product information is up to date with the current scientific knowledge including the conclusions of the assessments and recommendations made publicly available.

General Notes on ACO submission:

- The previous license of the product in Egypt shall be submitted.
- The ACO document shall be signed by the QPPV/Clinical expert.
- The period covered by the ACO shall be with date format day/month/year as following:
  - **Starting date of the period covered by the ACO:** Date of initial marketing authorization or the date of the last renewal of the product.
  - **Data Lock Point of the ACO:** 90 days prior to submission of renewal file to PHARMACEUTICAL VIGILANCE GENERAL ADMINISTRATION (1st submission)
- The stamped approved label shall be submitted in the ACO, besides the updated proposed SmPC (if any).
- All reference documents used to prepare such ACO that were used to define and classify the safety concerns and documents used to define the risk minimization activity **shall be submitted**, for example –but not restricted to-
  - Search results
  - Public assessment report.
  - The SmPC of the reference product.
  - Literatures
- In case the products were not marketed. MAH shall submit a statement (on MAH official paper) signed by CEO declaring that your product is not launched yet & never been marketed or sold by any tenders along with adequate justification.
- **Note:** In case of the biological products, the ACO shall cover 5 years

8. Signal Management

8.1. Introduction

This chapter provides terminologies and definitions concerning signal management process (see Annex I for the corresponding glossary of terms), general principles and guidance on the scientific and quality aspects of signal management process. In addition, it describes roles, responsibilities and procedural aspects in the setting of the signal management practices overseen by the pharmaceutical vigilance general administration – PVGA (formerly the Egyptian pharmaceutical vigilance center – EPVC), the pharmaceutical vigilance general administration.

MAHs may follow alternative signal management processes and terminologies but they shall encompass the general principles outlined in this GVP guideline.

The following references provide additional guidance relevant to signal management activities defined in this chapter:

- European Medicines Agency (EMA). EU GVP module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA, October 2017);
- World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed. Geneva, World Health Organization; 2018. [Online] (https://apps.who.int/iris/handle/10665/259959);
- World Health Organization. Global manual on surveillance of adverse events following immunization, 2016 update. Geneva: World Health Organization; 2016. [Online] (https://apps.who.int/iris/handle/10665/206144);
- World Health Organization. COVID-19 vaccines: safety surveillance manual. Geneva: World Health Organization; 2021. [Online]. (https://apps.who.int/iris/handle/10665/338400);
- Report of Council for International Organizations of Medical Sciences – CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010);
- Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Work Package 5 – Signal Management – Best Practice Guide (National Competent Authorities (NCAs) in EU Member States, June 2016).

8.1.1. Definitions and terminology

Signal: According to the WHO, signal is defined as the reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Signal is also interpreted as information arising from one or multiple sources, including observations and experiments which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. New aspects of a known association may include changes in the frequency, distribution (e.g., gender, age and country), duration, severity or outcome of the adverse reaction. A signal often relates to all pharmaceutical products containing the same active substance, including combination products. Some signals may only be relevant for a particular pharmaceutical

product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of pharmaceutical products.

Signal management: A set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a pharmaceutical product or whether known risks have changed, as well as any related recommendations, decisions, communications, and tracking.

The PVGA`s signal management process includes the following activities: signal detection, prioritization, signal validation, signal assessment and confirmation, recommendations for action and decision, and exchange of information and implementation. The signal management process covers signals arising from any source. The signal management process concerns all stakeholders involved in the continuous safety profile monitoring and benefit-risk evaluation of authorized pharmaceutical products as per the applicable regulations and well-established international guidelines.

Safety observation: A safety observation may originate from one or multiple sources, including, scientific literature. This safety observation justifies earliest judgment to evaluate existence/non-existence of a hypothesis suggesting a new potentially causal association, or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial (i.e., a potential signal).

Signal detection: The process of looking for and/or identifying potential safety signals from any source suggesting a new safety information or a new pattern of a known adverse drug reaction incompletely documented previously.

Signal prioritization: The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patient population or having public health impact or which may significantly affect the risk-benefit balance of the pharmaceutical product and thus require careful attention and management.

Signal validation: The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

The signal validation shall take into account the strength of the evidence, the previous awareness of the association and the clinical relevance (see subsection 8.2). The extent of evaluation performed during signal validation versus further assessment may vary among pharmaceutical vigilance general administration, other regulatory authorities and MAHs' internal procedures.

Signal assessment: The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or pharmaceutical product or whether known risks have changed. This review may

include nonclinical and clinical data and shall be as comprehensive as possible regarding the sources of information.

Signal status: It defines the final/primary status of a detected signal throughout the signal management process. Signal status can be marked as: 'non-validated – known', 'non-validated – other', 'Validated - for assessment', 'Assessed - for action', 'Assessed - no action', or 'Monitor'.

Non-validated signal: A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted. For tracking purposes, signal status may be marked as: 'non-validated – known' (i.e., labelled/listed, flagged in other regulatory documents (e.g., PBRER, RMP) or previously alerted by other regulatory authorities, etc.) or 'non-validated – other' (i.e., due to confounders more likely cause the risk, contradicting time to onset, poor disease prognosis, etc.).

Validated signal: A signal for which the signal validation process has concluded that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. For tracking purposes, signal status may be marked as: 'Validated - for assessment' (earlier within the signal management process), 'Assessed - for action', 'Assessed - no action', or 'Monitor'.

Confirmed/Verified signal: A validated signal which, following further assessment, has been determined to be "true" (i.e., a causal association can be established). For tracking purposes, signal status may be marked as: 'Assessed - for action'.

Emerging safety issue: A safety issue considered by a MAH to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the pharmaceutical product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Indeterminate signal: It is primarily a validated signal which is determined with further assessment to be inconclusive (i.e., a causal association cannot be established at that point of time) due to lack of information or insufficient specificity of data. In the context of risk management, it is considered as "*an untoward occurrence in which there is some basis for suspicion of an association with the pharmaceutical product of interest but where this association has not been confirmed*". For tracking purposes, signal is refuted and its status may be marked as ('Assessed - no action' or 'Monitor').

Pharmaceutical product: Any substance or combination of substances presented as having properties for treating or preventing disease in human beings. It is any substance or combination of substances which might be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Refuted signal: It is a validated signal upon further assessment is concluded to be "False" that a causal relationship between the occurrence of a risk and administration of drug of interest cannot be established at this point in time.

8.2. Structures and processes

8.2.1. Sources of data and information

Signals can arise from a wide variety of data sources. This potentially includes all scientific information concerning the use of pharmaceutical products and the outcome of the use, i.e., quality, non-clinical and clinical data, including pharmacovigilance and pharmacoepidemiological data.

The common data source for detecting safety signals includes spontaneous reporting systems (SRS). Guidance on the requirements for collection, data management and reporting of suspected adverse reactions associated with pharmaceutical products for human use authorized in Egypt can be found in GVP Chapter 6.

Other data sources often exploited for signal detection include scientific literature, public health programs (e.g., expanded program of immunization (EPI)), active surveillance systems, drug-use registries, and pregnancy prevention programme (PPP).

This chapter focusses mainly on signals originating from the monitoring of data from spontaneous reporting systems, however all relevant data sources shall be considered during signal detection and management process.

8.2.2. Signal detection

Detection of signals may be performed based on a review of individual case safety reports, from statistical analyses in large pharmacovigilance databases, or from a combination of both.

Signal detection shall follow a methodology which takes into account the nature of data and the characteristics (e.g., time on market, patient exposure, target population) as well as the type of pharmaceutical product concerned (e.g., vaccines products may for example require specific methodological strategies in alignment with the WHO and well-recognized international guidelines. Data from all appropriate sources shall be considered (see section 8.2.1). Clinical judgment and causality assessment shall always be applied.

Signal detection is often based on the monitoring of databases of suspected adverse reactions (i.e., SRSs) (e.g., marketing authorization holder databases, national database 'VigiFlow' and the World Health Organization (WHO) global database of reported adverse events of pharmaceutical products, VigiBase maintained by Uppsala Monitoring Centre (UMC)). Data in such SRSs refers to suspected adverse reactions which are not confirmed to be caused by the suspected pharmaceutical products. There might be other factors for a patient to develop the adverse event reported. Those databases also vary in size. Organizations, shall opt the appropriate signal detection method(s), accordingly.

Detailed guidance on methods of signal detection can be found in the report of CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010)

and the EU GVP module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA, 2017).

The signal detection method (qualitative/quantitative) shall be adequately documented by each organization (see section 8.3.6).

8.2.2.1. Qualitative signal detection

Signals from the qualitative avenue may be originated from individual case safety reports in SRSs, interventional/observational clinical studies, active surveillance systems, or safety observations generated from scientific literature monitoring. A single report a serious or severe adverse reactions (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant, or serious adverse event concerning children or pregnancy) may be sufficient to generate hypothesis and flag a signal.

A review of ICSRs for the purpose of signal detection shall consider the number of cases (after exclusion of duplicates) for a given drug–event combination (DEC), patient demographics, temporal association, clinical outcome in relation to drug continuation or discontinuation (i.e., de-/ re-challenge information), the suspected pharmaceutical product (including dose administered, dosage regimen, route of administration) and the suspected adverse reaction (including signs and symptoms, risk factors, epidemiological data).

8.2.2.2. Quantitative signal detection

When the pool to a safety database is too large to allow individual investigation of all incoming ICSRs, it is useful to calculate disproportionality statistics for the purpose of looking for high proportions of a specific adverse event with a given pharmaceutical product compared to the reporting of this event for all other pharmaceutical products. Disproportionality statistics (e.g., IC, ROR, PRR) take the form of a ratio of the proportion of spontaneous ICSRs of a specific adverse event with a specific pharmaceutical product to the proportion that would be expected if no association existed between the product and the event. The calculation of the expected value is based on ICSRs that do not contain the specific product and it is assumed that these ICSRs contain a diverse selection of products most of which will not be associated with the event.

Organization may adapt a formal set of rules for a signal detection algorithm (SDA), including specified thresholds. When these rules are satisfied for a given DEC, it is called a signal of disproportionate reporting (SDR). Then a decision needs to be made regarding whether further investigation is required. The appropriate choice of thresholds is fundamental to the success of the statistical signal detection process. Very low thresholds will result in large and potentially unmanageable numbers of SDRs to investigate with a higher probability of being false. This will also reduce the resources available for assessment of true SDRs. Too high thresholds will result in identification of adverse reactions being delayed or even entirely prevented.

8.2.3. Signal prioritization

Every organization shall consider prioritization throughout the whole signal detection and management process. The following can be considered for signal prioritization, for example:

- The severity, seriousness, outcome and reversibility of the adverse reaction and the potential for prevention;
- Whether signals suggest risks with an important impact public health and/or on the risk-benefit balance of the pharmaceutical product;
- Signals that may cause media attention and/or public concerns (e.g., adverse events following immunization particularly from mass campaigns);
- The patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate;
- Whether the signal is likely to apply to other substances of the same class of pharmaceutical products;
- The consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options;
- The expected extent of the regulatory intervention (e.g., addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation).

8.2.4. Signal validation and in-depth assessment

Signal validation aims at deciding if further assessment is needed. Signal validation shall focus on evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further assessment.

For signals originating from SRSs, important considerations shall ensure, as a minimum, that there is a compatible temporal association and the signal is not based on duplicate reports. There are many sources of duplicate reporting. Duplicate reports may be arisen by multiple HCPs of the same patient, as well as sending by the patients themselves. Reports that contain suspect drugs from different MAHs may be another source of duplication. Duplicate reports may be also arisen due to errors when transferring ICSRs between different systems or databases.

The following aspects shall be taken into account when conducting signal validation:

- Previous awareness, for example:
  - The extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet or may indicate a class effect;
  - Whether the association has already been assessed in a PBRER or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.
  - Similar flags from other regulatory authorities worldwide
- Strength of evidence based on the review of ICSRs data, for example:
  - Disproportionate reporting (as applicable),
  - Total number of reports (after excluding duplicate reports);
  - Additional cases reported with related MedDRA terms (e.g., other terms indicating clinical complications, syndromes, or different stages of the same reaction);
  - Quality of the data and their documentation, including the number of index/well-documented cases in terms of a compatible temporal association, positive de- and/or rechallenge, lack of confounders/potential alternative causes, and/or assessed as possibly

related by the reporting healthcare professional with supportive results of relevant lab investigations;
- Consistency of the evidence across cases (e.g., consistent time to onset, pattern with repeated observations of an association);
- Cases matching internationally agreed case definitions (e.g., Brighton collaboration case definitions for vaccines), RUCAM for defining cases of drug-induced liver injury (DILI));
- Presence of evidence for a dose-response relationship;
- Possible mechanism based on a biological and pharmacological plausibility;
- Number of cases in the context of patient exposure.

- If the investigated signal is validated during preliminary investigation, further signal assessment considering all available data shall be considered. Availability of other relevant information that provides further evidence for or against a causal association or a new aspect of a known association a richer set of data on the drug-event combination (DEC) under investigation may include:
  - Findings in the scientific literature regarding similar cases for the DEC of interest, including information on substances of the same pharmacological class;
  - Information from clinical trials or other types of clinical studies;
  - Information on the epidemiology of the adverse reaction or the underlying disease;
  - Experimental and/or non-clinical findings;
  - Healthcare databases (if available) that may provide information on characteristics of exposed patients and medicines utilization patterns.
- Other aspects of clinical relevance and context to be considered during signal assessment include, for example:
  - Reactions occurring in the context of drug-drug interactions;
  - Additional insight on a known adverse reaction, e.g., in terms of its severity, duration, outcome, incidence or management;
  - Seriousness and severity of the reaction;
  - Outcome and reversibility of the reaction.

8.2.5. Recommendation for action and exchange of information

Signal assessment results suggesting at least a possible causal association – involving new or changed risks – between the adverse reaction and the administration of the pharmaceutical product shall be communicated to all stakeholders, including concerned marketing authorization holders. (See section 8.3.5)

8.2.6. Quality requirements

Signal management is one of the critical pharmacovigilance processes. Signal management process and associated procedures shall be clearly documented to ensure that the process is functioning properly and effectively. The roles, responsibilities and required tasks shall be conducted by staff with appropriate qualifications and expertise to enable appropriate provisions and, when needed, improvement of the system. The MAH staff shall be specifically trained in signal management activities in accordance with their roles and responsibilities. The training

system and location of the training records shall be documented, curriculum vitaes and job descriptions shall be archived.

A system of quality management (see Chapter 1) shall be in place and applied to all PV functions, including signal detection and management activities. Detailed procedure(s) shall be developed, documented and implemented to be clear and standardized. This includes the rationale for method(s) and periodicity of signal detection activities.

Marketing authorization holder shall include the description of the signal management process in the pharmacovigilance system master file (see Chapter 2). Appropriate performance indicators shall be controlled and presented in the relevant annex to the pharmacovigilance system master file (see GVP Chapter 2). Through a proper tracking system, MAH shall keep an audit trail of its signal detection and management activities and outcomes, including how signals have been detected, validated, and assessed.

8.3. Operation in Egypt

This subsection defines the roles and responsibilities of stakeholders concerned with this guideline, signal confirmation and further assessment by PVGA, notifications and procedural options for validated signals by MAHs, emerging safety issues in signals, inclusion of signal in PBRER, the recommendation for actions, and signal record management.

8.3.1. Roles and responsibilities of the marketing authorization holder operating

In the context of signal detection and management requirements, the marketing authorization holder shall continuously monitor the safety of its pharmaceutical products. Signals detected through different sources shall be handled according to the marketing authorization holder's own signal management process, taking into account the general principles outlined in module IX.B of the EU GVP guidelines.

The MAH shall inform PVGA of any changes that might have an impact on the marketing authorization. This includes information on signals that meets the definition of emerging safety issues.

The marketing authorization holder:

- Shall monitor the data in its own safety database. The frequency of the monitoring shall be at frequencies proportionate to the products' safety profile as well as to the importance of identified or potential risk and the need for additional monitoring and/or additional risk minimization activities;
- Shall validate and evaluate the detected signals and notify PVGA with the validated or confirmed signals according to the timelines mentioned in this guideline (see section 8.3). The MAH shall take into account the essentials of signal validation referenced in section 8.2. MAH shall consider the requirements to keep their products' safety profiles up-to-date throughout the product's lifecycle in the light of latest scientific knowledge and to present signal information in corresponding PBRERs reporting periods;
- For non-referenced biosimilar and innovative products with at least one domestic ICSR reported in the territory, MAH shall validate, evaluate, and notify PVGA, irrespective of the final signal status (confirmed, monitor or refuted);

- For potential signals that have a significant impact on the benefit-risk balance for a pharmaceutical product and/or have implications for public health (i.e., meeting the definition of emerging safety issues), MAH shall adhere with the provisions and timelines outlined in section 8.3 and chapter 10 of this guideline;
- Shall collaborate with PVGA for the assessment of the validated signals by providing supplementary data upon request;
- Shall keep and maintain an audit trail for its signal detection and management activities;
- Shall evaluate the effectiveness of the additional risk minimization measures imposed on its pharmaceutical products post-signal assessment steps and shall inform PVGA with results upon request.

8.3.2. Roles and responsibilities of the pharmaceutical vigilance general administration (PVGA) being the national pharmacovigilance center and PV regulator in Egypt

Pharmaceutical vigilance general administration shall continuously monitor the safety of active substances/pharmaceutical products authorized at the local market that is available in its national database of individual case safety reports (ICSRs), which is called 'VigiFlow'. This is to determine whether there are new risks or whether risks have changed patterns and whether those risks have an impact on the benefit-risk balance. Pharmaceutical vigilance general administration shall consider risk-based approach for prioritizing and validating the detected signals originated in the territory from any source and confirming for further assessment in accordance with the principles outlined in this guidance, and with reference to documents mentioned in the introduction of this chapter. Examples of potential signals to be prioritized for the validation phase are:

- Any product considered to have an identified or potential risk that could impact significantly on the benefit-risk balance or have implications for public health. This may include risks associated with drug-use issues (medication errors, overdose, misuse, abuse, off-label use);
- Any product for which the safety information is limited due to low patient exposure during drug development, including products authorized under conditional approval or under exceptional circumstances, emergency use, or for which there are vulnerable or poorly studied patient populations or important missing information (e.g., pediatrics, pregnant women, renal-impaired patients) while post-marketing exposure is likely to be significant;
- Any biosimilar product or any product contains new innovate active substance authorized for emergency use;
- Any product indicated for use in a new patient population or with a new route of administration;
- Any product for which the existing marketing authorization has been significantly varied (e.g., changes to indication, posology, pharmaceutical form or route of administration), thereby modifying the exposed patient population or the safety profile.

As applicable, PVGA shall take the appropriate regulatory actions following the signal assessment to maintain the positive benefit-risk ratio of pharmaceutical products authorized at the local market.

In specific situations, PVGA may decide to not further assess and confirm a validated signal if, for instance:

1. The validated signal involves an adverse drug reaction that is already adequately reflected in the product information of other pharmaceutical products authorized Egypt with the same active substance;
2. The signal has already been subject of review and the data that has arisen since this review does not provide substantial new evidence;
3. The signal subject of current review by one or more regulatory authorities of the listed reference countries that are formally relied by EDA.

Generally, PVGA can collaborate with the concerned marketing authorization holder(s) by requesting supplementary data and inform them about the conclusions, outcomes and decision of the assessed signals.

PVGA shall monitor the PV practices of concerned MAHs in implementing additional risk minimization measures imposed on their pharmaceutical products after signal assessment and confirmation. Additionally, PVGA shall evaluate the extent of effectiveness for the implemented additional risk minimization measures by concerned MAHs and take the necessary actions as needed.

PVGA shall perform a regular review of its signal management methodology in accordance with the latest well-respected international guidelines and best PV practices and scientific knowledge in relation to causality assessment methods and signal management activities.

PVGA shall keep and maintain a signal tracker for its signal detection and management activities, including, validated signals that require further assessment.

8.3.3. Signal confirmation and further assessment by PVGA

PVGA has the responsibility to confirm in a timely manner the validated signals originated from spontaneous safety reports captured in the national safety database 'VigiFlow' or any other data source whenever a further signal assessment is warranted. PVGA may further adjust the signal scope by extending it to other active substances of the same class of pharmaceutical products, other pharmaceutical products for active substances of different pharmacological classes or to other related adverse reactions/medical conditions. Templates for relevant PVGA's signal evaluation reports (new/follow-up signal) shall be in place.

The assigned signal assessor shall comprehensively evaluate, propose recommendation for action(s), present signal in-depth assessment results on EDA's national pharmacovigilance committee and communicate decisions to the concerned MAH(s), as appropriate.

Marketing authorization holders shall collaborate with PVGA for the purposes of confirming and in-depth assessing the validated signals. This can be via releasing PVGA's requests for supplementary data to the concerned MAH. Requests for additional data are sent to the qualified person responsible for pharmacovigilance (QPPV) of the concerned MAH. QPPV details are identified based on the information provided by MAHs in the context of obligations detailed in this GVP guideline (see Chapter 1).

PVGA may request supplementary data, including, a cumulative review/comprehensive signal investigation of relevant data (e.g., from spontaneous reporting systems, scientific literature,

clinical trials) together with a discussion and conclusion from any concerned MAH within defined timeliness. These timelines usually encompass 2 months for submission of responses by the concerned MAHs. However, where appropriate, longer or shorter timelines may apply. The MAH(s) shall submit the required supplementary data through the proper PVGA's reception portal specified for such purposes. If the MAH is unable to provide the requested data on time, it shall inform the pharmaceutical vigilance general administration's signal management unit in writing as early as possible in advance of the due date. A justification for requesting grace period extension shall be provided and a new submission date proposed.

It shall take into account that pharmaceutical vigilance general administration may request from the concerned MAH of the innovative product/brand such additional information as it is expected to hold the most comprehensive safety data on the corresponding active substance or active ingredient variant.

8.3.4. Notifications and procedural options for validated signals by a marketing authorization holder based on the continuous monitoring of PV data from any data source

8.3.4.1. Standalone signal notification

When a marketing authorization holder concludes that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis of the signal (i.e., having 'validated signal') based on its preliminary assessment of a signal detected from any data source for its authorized pharmaceutical product and does not meet the criteria outlined in this subsection, the MAH shall submit a standalone signal notification according to the mechanisms of notification listed in Table 1.

A standalone signal notification shall be sent after the MAH has validated the detected signal within a timeline no later than 45 calendar days. The MAH shall send to PVGA a follow-up notification within a timeline no later than 45 calendar days upon completion its signal assessment for non-referenced biosimilars or innovative products regardless the final concluded status (confirmed/indeterminate/refuted). The MAH shall submit its standalone signal notifications by adequately fill in the required fields of the form available at relevant pharmaceutical vigilance general administration's signal reception portal alongside providing the required attachments, as appropriate.

8.3.4.2. Emerging safety issue (ESI) signals

All validated signals that detected from any source and meet the definition of emerging safety issues that require urgent attention (ESI), including quality defects with/without clinical consequences shall only be reported by the MAH as emerging safety issues to the relevant pharmaceutical vigilance general administration's reception portal within the required timeline (refer to chapter 10 'Safety communication'). This also includes the ICSRs submission requirements when the emerging safety issue refers to a single case of suspected adverse reaction(s).

When notifying an ESI, the MAH shall describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and shall provide any relevant documentation available at the time of initial notification. Any further information relevant to the issue shall be provided to the PVGA as soon as it becomes available. Generally, the MAHs shall collaborate with PVGA in assessment of emerging safety issues. For detailed PV requirements in relation to processing of emerging safety issues, refer to chapter 10 of this GVP guideline.

Standalone notifications for this type of validated signals (i.e., ESI signals) are not required. Unless it is found to be appropriate to handle the ESI within PVGA's signal management process, in which case the concerned MAH may be requested to provide additional information and/or standalone signal notification supplemented by a comprehensive signal evaluation report (SER) in case of non-referenced biosimilar or innovative products.

8.3.5. Recommendation for actions on signals from the pharmaceutical vigilance general administration

After a comprehensive assessment of validated signals and discussion by EDA's national pharmacovigilance committee, the pharmaceutical vigilance general administration (PVGA) may decide any or a combination of the following actions:

- The MAH shall provide supplementary data (e.g., comprehensive signal evaluation report with/without specific assessment considerations) within a signal procedure;
- The MAH shall provide an additional data or a cumulative review on the signal in the following PBRER or submit an ad-hoc PBRER;
- The MAH shall update the product safety information according to the applicable regulations for variation procedures by referral to requirements imposed by the pharmacology committee of EDA;
- The MAH shall submit an updated risk management plan (RMP) for its authorized pharmaceutical product;
- The MAH shall implement additional risk minimization measures such as local distribution of educational materials or the dissemination of a direct healthcare professional communication (DHPC);
- The MAH shall sponsor a post-authorization safety study (PASS) according to an agreed protocol and subsequently submit the final results of that study;
- Other EDA scientific committees or higher technical committees shall be consulted to adopt national pharmacovigilance committee recommendations (e.g., adding products containing a specific active pharmaceutical ingredient (API) into the list of controlled substances, suspending the authorized product use, market withdrawal, restriction of product administration for a specific indication, patient sub-population, or route of administration, etc.);
- The raised signals of vaccine products can be presented to the National Causality Committee (NCC) of the Egyptian ministry of health and population (MoHP), if required.

- A pharmacovigilance inspection shall take place in order to verify that the marketing authorization holder for the pharmaceutical product satisfies the pharmacovigilance requirements as endorsed by the applicable laws, decrees and related regulations;
- PVGA shall collect further information from relevant stakeholders inside EDA or perform additional signal analyses;
- Any other appropriate action that is not listed above;
- No action is required at this point in time, other than routine pharmacovigilance.

At any point in time, PVGA can independently request from the concerned MAHs supplementary data in the context of its routine signal procedures. As appropriate, PVGA can directly endorse and communicate regulatory actions to the concerned MAH or endorse penalties based on MAH's PV non-compliance within the scope of signal management requirements.

8.3.6. Signal record management

PVGA – as being the responsible entity of the national pharmacovigilance system and PV regulations within EDA – shall keep a signal tracker of all its internal signal management activities in line with the principles outlined in this guidance, and with referral to relevant guidelines and guidance for best practices. PVGA has the responsibility to keep an audit trail for signal communications, decisions, actions and timelines with different stakeholders. This also includes signal notifications by MAHs, relevant inquiries and outcomes, as appropriate.

Marketing authorization holder shall put in place a record management system for all pharmacovigilance functions – involving signal detection and management activities – that ensures the retrievability of corresponding documents as well as the traceability of the measures taken to investigate safety concerns, timelines for those investigations and decisions on safety concerns, including dates and the decision-making process. As for any critical process, signal management process shall be audited at regular intervals, including tasks performed by any service providers and third parties. Data and document confidentiality (per the applicable laws and regulations), security and validity (including data integrity when transferred between organizations) shall be guaranteed.

Table 1. Mechanisms of flow for standalone signal notifications received from marketing authorization holders.

* Domestic ICSR(s)	MAH's product type	Registered by reference/stringent authority?	Signal status	Exchange of information	Expected timelines
No domestic case(s)	Innovator / Biosimilar / Generics	Yes/No	Validated	- MAH shall submit a notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the	No later than 45 calendar days from signal validation date.

				filled submission form. - No further replies from PVGA will be sent to MAH unless supplementary data is required.	
No domestic case(s)	Innovator / Biosimilar / Generics	Yes/No	Confirmed signal	- MAH shall submit a follow-up notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the filled submission form. - No further replies from PVGA will be sent to MAH unless supplementary data is required.	No later than 45 calendar days from the date of signal assessment completion.
Domestic case(s) is/are available	Generics	Yes/No	Validated	- MAH shall submit a notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the filled submission form. - No further replies from PVGA will be sent to MAH unless supplementary data is required.	No later than 45 calendar days from signal validation date.
Domestic case(s)	Generics	Yes/No	Confirmed signal	- MAH shall submit a follow-	No later than 45

is/are available				up notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the filled submission form. - No further replies from PVGA will be sent to the MAH unless supplementary data is required.	calendar days from the date of signal assessment completion.
Domestic case(s) available	Innovator / Biosimilar	Yes	Validated	- MAH shall submit a notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the filled submission form. - No further replies from PVGA will be sent to the MAH unless supplementary data is required.	No later than 45 calendar days from the signal validation date.
Domestic case(s) available	Innovator / Biosimilar	Yes	Completed signal assessment [Confirmed/Monitor/Refuted]	- MAH shall submit a follow-up notification on the PVGA's portal for standalone signal notifications. - MAH will only receive a confirmation email for the filled	No later than 45 calendar days from the date of signal assessment completion.

				submission form. - No further replies from PVGA will be sent to the MAH unless supplementary data is required.	
Domestic case(s) is/are available	Innovator / Biosimilar	No	Validated	- MAH shall submit a notification on the PVGA's portal for standalone signal notifications. - MAH will receive a confirmation email for the filled submission form - PVGA will send to the MAH a "RECEIPT" e-mail within 5 business days from receiving this type of signal notification. - Further PVGA communication will be released to the MAH.	No later than 45 calendar days from the signal validation date.
Domestic case(s) is/are available	Innovator / Biosimilar	No	Completed signal assessment [Confirmed/Monitor/Refuted]	- MAH shall submit a follow-up notification on the PVGA's portal for standalone signal notifications. - The corresponding SER shall be provided during the submission process of standalone signal notification on the PVGA reception portal.	No later than 45 calendar days from the date of signal assessment completion.

				- MAH will receive a confirmation email for the filled submission form. - PVGA will send to the MAH a "RECEIPT" e-mail within 5 business days from receiving this type of signal notification. - Further PVGA communication will be released to the MAH.	

Abbreviations:
PVGA: Pharmaceutical Vigilance General Administration; MAH: Marketing Authorization Holder; SER: Signal Evaluation Report.

N.B.
***** Domestic ICSR refers to at least one case reported in Egypt concerning MAH''s notified signal.
* If the notified signal meets the criteria of an emerging safety issue (ESI), no standalone signal notification is required and the MAH shall comply with the required timelines for notifying ESIs.

9. Post authorization Safety Studies

9.1. Introduction

A post-authorization safety study (PASS) is defined as any study relating to an authorized pharmaceutical product conducted with the aim of identifying, characterizing or quantifying a safety hazard or a lack of efficacy, confirming the safety profile of the pharmaceutical product, or measuring the efficacy of a product in post-marketing setting, or measuring the effectiveness of risk management measures.

A PASS may be initiated, managed or financed by a marketing authorization holder voluntarily, or pursuant to an obligation imposed by EDA.

This chapter concerns PASS which are clinical trials or non-interventional studies and does not address non-clinical safety studies.

A PASS is non-interventional if the following requirements are cumulatively fulfilled:

- The pharmaceutical product is prescribed in the usual manner in accordance with the terms of the marketing authorization.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data).

Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

If a PASS is a clinical trial (i.e. interventional study); the national regulation for clinical trials and the national rules governing interventional clinical trials of pharmaceutical products in Egypt shall be followed.

The purposes of this chapter are to:

- Provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorization holders voluntarily or pursuant to an obligation imposed by EDA.
- Describe procedures whereby EDA may impose to a marketing authorization holder an obligation to conduct a clinical trial or a non-interventional study, and the impact of this obligation on the risk management system.

- Describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results, and for changes to the marketing authorization following results.

Methods for PASS

- **Active surveillance**
  - Intensive monitoring
  - Prescription Event Monitoring
  - Registries
  - Others…
- **Observational studies**
  - Cross sectional
  - Cohort Monitoring
  - Case-control
  - Others…

Triggers for conducting Active surveillance by EDA or as an obligation to MAH:

- Conducting Active surveillance is to portray the ongoing patterns of an ADR(s) occurrence to a specific product with a specific safety concern, and no available safety data present in the national or global database, so that investigation, control, and prevention measures can be applied efficiently and effectively to guide interventions on the registration status of the product.

- This is mainly proposed by the **technical committee of EDA**, the **national pharmacovigilance committee** of EDA, within a **joint multi-country surveillance** after the approval of EDA chairman, or as a recommendation from the Egyptian expanded program for immunization for the **Adverse events of special interests**.

9.2. Structures and processes

9.2.1. Scope

This guidance applies to **non-interventional PASS** which are initiated, managed or financed by a marketing authorization holder and conducted in Egypt, or outside Egypt which have been imposed or required by EDA. Where applicable, legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to studies conducted voluntarily in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format of study protocols, abstracts and final study reports and to the communication of study information to EDA. Where relevant, a distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation.

This guidance applies to studies initiated, managed or financed by a marketing authorization holder as well as those conducted by a third party on behalf of the marketing authorization holder.

This guidance applies to studies that involve primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.

9.2.2. Terminology

Date at which a study commences: date of the start of data collection.

Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.

End of data collection: the date from which the analytical dataset is completely available.

Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan.

9.2.3. Principles

A post-authorization study shall be classified as a PASS when the main aim for initiating the study includes any of the following objectives:

1. To quantify potential or identified risks, e.g., to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another pharmaceutical product, and investigate risk factors, including effect modifiers;
2. To evaluate the risks of a pharmaceutical product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups; newly introduced in the market)
3. To evaluate the risks of a pharmaceutical product after long-term use;
4. To provide evidence about the absence of risks;
5. To assess patterns of medicines utilization that add knowledge regarding its safety or appropriateness of risk management measures (e.g. information on indication, off-label use, dosage, co-medication or medication errors in clinical practice)

Whereas the PASS design shall be appropriate to address the study objective(s), the classification of a post-authorization study as a PASS is not constrained by the type of design chosen if it fulfils the criteria as set in definition of the PASS. For example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

Relevant scientific guidance shall be considered by marketing authorization holders and investigators for the development of study protocols, the conduct of studies and the writing of study reports, and by national medicines authorities for the evaluation of study protocols and study reports. Relevant scientific guidance includes the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the Guideline on Conduct of

Pharmacovigilance for Medicines Used by the Pediatric Population for studies conducted in children, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP).

For studies that are funded by a marketing authorization holder, including studies developed, conducted or analyzed fully or partially by investigators who are not employees of the marketing authorization holder, the marketing authorization holder shall ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorization holder and investigators shall ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process. In the research contract, the marketing authorization holder shall consider the provisions of the ENCePP Code of Conduct, and address the following aspects:

- Rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- Rights and obligations of the investigator(s) and marketing authorization holder;
- Clear assignment of tasks and responsibilities;
- Procedure for achieving agreement on the study protocol;
- Provisions for meeting the marketing authorization holder ‘s pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
- Intellectual property rights arising from the study and access to study data;
- Storage and availability of analytical dataset and statistical programs for audit and inspection;
- Communication strategy for the scheduled progress and final reports;
- Publication strategy of interim and final results.

Non-interventional post-authorization safety studies shall not be performed where the act of conducting the study promotes the use of a pharmaceutical product. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the marketing authorization holder and by third parties on behalf of the marketing authorization holder.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred.

9.2.4. Protocol:

All post-authorization safety studies shall have a written study protocol before the study commences. The study shall follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. National requirements shall be followed for ensuring the well-being and rights of the participants. The marketing authorization holder is required to submit the protocol to the general administration of pharmaceutical vigilance. The marketing authorization holder ‘s pharmacovigilance contact person in Egypt shall be informed of any study sponsored or conducted by the marketing authorization holder, and shall be shall be involved in the review and sign-off of study protocols conducted. Any requirements requested by EDA within the study period shall be fulfilled by the marketing authorization holder and the responsible pharmacovigilance person.

9.2.4.1. Format and content of study protocol:

The study protocol shall include the following information:

1. **Title**: informative title including a commonly used term indicating the study design and the pharmaceutical product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.
2. **Marketing authorization holder**: name and address of the marketing authorization holder.
3. **Responsible parties**: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators shall be made available to EDA upon request.
4. **Abstract**: stand-alone summary of the study protocol including the following sub-sections:
    - Title with subtitles including version and date of the protocol and name and affiliation of main author
    - Rationale and background
    - Research question and objectives
    - Study design
    - Population
    - Variables
    - Data sources
    - Study size
    - Data analysis
    - Milestones
5. **Amendments and updates**: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
6. **Milestones**: table with planned dates for the following milestones:
    - Start of data collection
    - End of data collection
    - Study progress report(s) as
    - Interim report(s) of study results, where applicable, in line with phases of data analyses
    - Final report of study results

    Any other important timelines in the conduct of the study shall be presented.
7. **Rationale and background**: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review shall cite the findings of similar studies, and the expected contribution of the current study.
8. **Research question and objectives**: research question that explains how the study will

address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.

9. **Research methods**: description of the research methods, including:

9.1. **Study design**: overall research design and rationale for this choice.

9.2. **Setting**: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods shall be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies shall be explained.

9.3. **Variables**: outcomes, exposures and other variables including measured risk factors shall be addressed separately, including operational definitions; potential confounding variables and effect modifiers shall be specified.

9.4. **Data sources**: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study shall be presented. If a pilot study has already been performed, a summary of the results shall be reported. Involvement of any expert committees to validate diagnoses shall be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators shall be described.

9.5. **Study size**: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

9.6. **Data management**: data management and statistical programs to be used in the study, including procedures for data collection, retrieval and preparation.

9.7. **Data analysis**: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorize, analyze and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

9.8. **Quality control**: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programs. As appropriate, certification and/or qualifications of any supporting laboratory or research groups shall be included.

9.9. **Limitations of the research methods**: any potential limitations of the study design,

data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors shall be discussed.

10. **Protection of human subjects**: safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.
11. **Management and reporting of adverse events/adverse reactions**: procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.
12. **Plans for disseminating and communicating study results,** including any plans for submission of progress reports and final reports.
13. **References:** The format of the study protocol shall follow the Guidance for the format and content of the protocol of non-interventional post-authorization safety studies.

Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, shall be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report shall be made available to EDA upon request. Feasibility studies that are part of the research process shall be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

An annex shall list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

9.2.4.2. Substantial amendments to the study protocol

The study protocol shall be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start shall be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, EDA shall be informed immediately and the study shall subsequently be conducted in accordance with the National Rules Governing Clinical Trials by EDA.

9.2.5. Reporting of pharmacovigilance data to EDA:

Data relevant to the risk-benefit balance of the product

The marketing authorization holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the pharmaceutical product concerned. Any new information that may affect the risk-benefit balance of the pharmaceutical product shall be communicated immediately in writing as an Emerging Safety Issue to the pharmaceutical vigilance general administration. Information affecting the risk-benefit balance of the pharmaceutical product may include that arising from an analysis of adverse reactions and aggregated data.

This communication shall not affect information on the results of studies which shall be provided by means of periodic benefit risk evaluation reports (PBRERs) and in RMP updates, where applicable.

9.2.5.2. Reporting of adverse reactions/adverse events

Adverse reactions/adverse events shall be reported the pharmaceutical vigilance general administration. Procedures for the collection, management (including a review by the marketing authorization holder if appropriate) and reporting of suspected adverse reactions/adverse events shall be put in place and summarized in the study protocol. If appropriate, reference can be made to the Pharmacovigilance System Master File but details specific to the study shall be described in this section. For study designs where expedited reporting is not required, this shall be stated in the study protocol.

9.2.5.3. Study reports

Progress reports

Progress reports may be requested by the pharmaceutical vigilance general administration. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of risk-benefit information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

The timing of the progress reports shall be agreed with the pharmaceutical vigilance general administration and specified in the study protocol when they have been agreed before the study commences. Study progress shall also be reported in any periodic benefit risk evaluation reports (PBRERs), and risk management plan (RMP) updates, where applicable.

The content of the progress report shall follow a logical sequence and shall include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report of study results. After review of the report, additional information may be requested.

Final study report

The final study report shall be submitted as soon as possible within 12 months of the end of data collection.

If a study is discontinued, a final report shall be submitted and the reasons for terminating the study shall be provided.

The final study report shall include the following information:

1. **Title**: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author.
2. **Abstract**: stand-alone summary in the format presented below.
3. **Marketing authorization holder**: name and address of the marketing authorization holder.

4. **Investigators**: names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators shall be made available to EDA upon request.

5. **Milestones**: planned and actual dates for the following milestones:

    - Start of data collection
    - End of data collection or date of early termination, if applicable, with reasons for termination
    - Study progress report(s)
    - Interim report(s) of study results, where applicable
    - Final report of study results
    - Any other important milestone applicable to the study, including date of protocol approval by an Institutional Review Board/Independent Ethics Committee if applicable, and date of study registration in the National PAS Register.

6. **Rationale and background**: short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.

7. **Research question and objectives**: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.

8. **Amendments and updates to the protocol**: list of any substantial amendment and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.

9. **Research methods**:

    9.1. Study design: key elements of the study design and the rationale for this choice.

    9.2. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.

    9.3. Subjects: any source population and eligibility criteria of study subjects. Sources and methods of selection of participants shall be provided, including, where relevant methods

    for case ascertainment, as well as number of and reasons for dropouts.

    9.4. Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.

    9.5. Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In case of a systematic review or meta-

analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

9.6. Bias: any efforts to assess and address potential sources of bias.

9.7. Study size: study size, rationale for any sample size calculation and any method for attaining projected study size.

9.8. Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

9.9. Statistical methods: description of:

- Main summary measures
- Statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
- Any methods used to examine subgroups and interactions
- How missing data were addressed
- Any sensitivity analyses
- Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

9.10. Quality control: mechanisms to ensure data quality and integrity.

10. Results: presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results shall be presented. Precision of estimates shall be quantified using confidence intervals. This section shall include the following sub-sections:

10.1. Participants: numbers of study subjects at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.

10.2. Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

10.3. Outcome data: numbers of participants across categories of main outcomes.

10.4. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk shall be translated into absolute risk for a meaningful time period.

10.5. Other analyses: other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.

10.6. Adverse events and adverse reactions: summary of all adverse events/adverse

reactions reported in the study, in line with requirements described in Chapter VI. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this shall be stated.

11. **Discussion**:

    11.1. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorization safety study, and, where relevant, impact of the results on the risk-benefit balance of the product.

    11.2. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases shall be discussed.

    11.3. Interpretation: interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

    11.4. Generalizability: the generalizability (external validity) of the study results.

12. **References**.

13. **Other information**: any additional or complementary information on specific aspects not previously addressed.

The format of the final study report shall follow the Guidance for the format and content of the final study report of non-interventional post-authorization safety studies.

The abstract of the final study report shall include a summary of the study methods and findings presented in the following format:

1. Title, with subtitles including date of the abstract and name and affiliation of main author;
2. Keywords (not more than five keywords indicating the main study characteristics);
3. Rationale and background;
4. Research question and objectives;
5. Study design;
6. Setting;
7. Subjects and study size, including dropouts;
8. Variables and data sources;
9. Results;
10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk-benefit balance of the product);
11. Marketing authorization holder;
12. Names and affiliations of principal investigators.

9.2.6. Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorization holder, the marketing authorization holder and the investigator shall agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorization holder shall be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. the marketing authorization holder shall communicate to the pharmaceutical vigilance general administration the final manuscript of the article within two weeks after first acceptance for publication.

9.2.7. Data protection

Marketing authorization holders and investigators shall follow the Egyptian legislation and guidance.

For PASS imposed as an obligation, the marketing authorization holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected. This provision shall also be applied to PASS voluntarily initiated, managed or financed by the marketing authorization holder.

9.2.8. Quality systems, audits and inspections

The marketing authorization holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the marketing authorization holder shall ensure that the analytical dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision shall also be applied to PASS voluntarily initiated, managed or financed by the marketing authorization holder.

9.2.9. Impact on the risk management system

Non-interventional PASS imposed as an obligation or required to investigate a safety concern of the RMP shall be described in the RMP Part III. Protocols for studies in the pharmacovigilance plan shall be provided in RMP annex 6 until submission of the final study report to the pharmaceutical vigilance general administration. Studies looking at the effectiveness of risk minimization measures shall be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimization plan.

Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product shall be listed in the RMP section III —Summary table of additional pharmacovigilance activities.

9.3. Operation in Egypt

This section provides guidance on procedures for imposing PASS, roles and responsibilities of stakeholders concerned with this guideline, and changes to marketing authorization following results from a non-interventional PASS.

9.3.1. Procedure for imposing post-authorization safety studies

The conduct of any post-authorization safety study (PASS) can be imposed during the evaluation of the initial marketing authorization application or during the post-authorization phase by EDA whenever there are concerns about the risks of an authorized pharmaceutical product. This obligation shall be duly justified based on benefit-risk considerations, shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study. The request may also include recommendations on key elements of the study (e.g. study design, setting, exposure(s), outcome(s), study population).

a. Request for a post-authorization safety study as part of the initial marketing authorization application

A marketing authorization may be granted by EDA to the conduct of a PASS.

b. Request for a post-authorization safety study during a post-authorization regulatory procedure

The need for a PASS could be identified by EDA during a post-authorization regulatory procedure, for example, an extension or a variation to a marketing authorization or a renewal procedure.

c. Request for a post-authorization safety study due to an emerging safety concern

After the granting of the marketing authorization, EDA, where applicable, may impose on the marketing authorization holder an obligation to conduct a post-authorization safety study if there are concerns about the risk of the authorized pharmaceutical product, for example following evaluation of a safety signal.

d. Joint post-authorization safety studies

If safety concerns apply to more than one pharmaceutical product, EDA may, if applicable, encourage the marketing authorization holders concerned to conduct a joint PASS. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorization holders shall contain the justification for the request of a joint study and the elements of the study design that support a joint protocol. Upon request from the marketing authorization holders, EDA may organize a pre-submission meeting in order to provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, EDA may define, in consultation with the relevant committee, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorization holder will have to implement in the study protocol to be submitted to EDA.

e. Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of the obligation, the marketing authorization holder may request the opportunity to present written observations in response to the imposition of the obligation. EDA shall specify a time limit for the provision of these observations. On the basis of the written observations submitted by the marketing authorization holder, EDA shall withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorization shall be subject to variation to include the obligation as a condition and the risk management plan (RMP), where applicable, shall be updated accordingly.

9.3.2. Regulatory supervision of non-interventional post-authorization safety studies

Non-interventional PASS conducted pursuant to obligations imposed by EDA are supervised and assessed by the pharmaceutical vigilance general administration, and national pharmacovigilance committee, as appropriate. Necessary approvals from the national scientific research ethics committee shall be obtained as well.

9.3.2.1. Roles and responsibilities of the marketing authorization holder

Following the imposing of the obligation to conduct a non-interventional PASS as a condition to the marketing authorization, the marketing authorization holder shall develop a study protocol and submit it to the pharmacovigilance general administration.

The marketing Authorization holder shall submit, along with the study protocol, the qualifications of the principal investigator, sub-investigators, and those who are involved in the PASS conduction, and signed agreement/ contract between involved parties to the pharmacovigilance general administration.

The marketing authorization holder has the responsibility to ensure that the study is not a clinical trial, and meet the requirements applicable to non-interventional PASS. The marketing authorization holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

The marketing authorization holder shall develop the study protocol following the format described in the guidance for the format and content of the protocol of non-interventional post-authorization safety studies, and shall consider the recommendations set out. The study may commence only when the written endorsement from the national scientific research ethics committee has been issued. When a letter of endorsement has been issued by the national scientific research ethics committee, the marketing authorization holder shall notify the pharmaceutical vigilance general administration of the approval and may thereafter commence the study according to the endorsed protocol. National requirements shall be followed to ensure the well-being and rights of participants in the study.

After a study has been commenced, the marketing authorization holder shall submit any substantial amendments to the protocol, before their implementation, to the pharmaceutical vigilance general administration and the national scientific research ethics committee, as appropriate for the definition of substantial amendment.

The marketing authorization holder may be requested to submit the study progress reports to the pharmaceutical vigilance general administration in which the study is conducted.
Upon completion of the study, the marketing authorization holder shall submit a final study report, including a public abstract, to the pharmaceutical vigilance general administration / national scientific research ethics committee as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by EDA, the marketing authorization holder shall request the waiver in writing at least three months before the due date for the submission of the report, the waiver request may be granted or rejected on the basis of the justification and timeline submitted by the marketing authorization holder. The final study report shall follow the format described for the format and content of the final study report of non-interventional post-authorization safety studies.

9.3.2.2. Roles and responsibilities of EDA

EDA will inform the marketing authorization holder in writing and within the appropriate timelines of its decisions with respect to the assessment of the following:

- Study protocol;
- Study protocol amendments;
- Final study report;
- Waiver request for the submission of the final study protocol

EDA is responsible for inspecting research sites in which the PASS is conducted as well as other related entities with a view to verify compliance with GCP. For this purpose, EDA has the right to accomplish the following:

1- Preparing an inspection plan on the research sites in which the research is conducted as well as other related entities
2- Examining and reviewing the documents, installations, records, and other sources related to clinical medical research.
3- Ensuring the research protocol implementation and verifying GCP compliance.
4- Ensuring the application of the domestically and internationally recognized standards of GCP.
5- Monitoring any observations or violations, and preparing a report of the inspection findings.
6- Following up and assessing the periodic reports concerning the clinical medical research under study.

The inspection plan for PASS is prepared according to risk based approach. EDA may conduct an inspection at any stage of the PASS whether before study initiation, during study conduction or after the end of the study to ensure compliance with GCP guidelines.

Inspection Plan notification:

- For Routine Inspection:

The applicant will be notified within two weeks before the proposed date of inspection. The applicant shall confirm the availability of the PI and/or Co-PI(s) and other study personnel (required as per the scope of inspection) at the proposed date. Upon affirmation, the inspection agenda and confirmation letter will be sent to the PI through the applicant.

- For Triggered Inspection:

In the case of triggered inspection, the applicant may be notified within 24 hours before the inspection date.

- For Follow up Inspection:

Follow-up inspection can be carried out either to ensure the corrective action(s) &/or preventive action(s) implementation or after any applied amendments approved by EDA. The applicant will be notified within one week before the proposed date of inspection.

Inspection Report:

The inspection report will be sent to the applicant within 15 days after the inspection. The findings in the inspection report are classified into critical, major, or minor.

Critical GCP findings, Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data, and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

Major GCP findings, Observations classified as major may include a pattern of deviations and/or numerous minor observations.

Minor GCP findings, Observations classified as minor indicate the need for improvement of conditions, practices, and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Corrective Action and Preventive Action (CAPA) Plan: The applicant shall prepare the corrective and preventive actions plan within the timeframe mentioned from receiving the inspection report from EDA.

10. Safety communication

10.1. Introduction

This Chapter describes how to communicate and coordinate safety information concerning pharmaceutical products authorized in Egypt. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimizing risks and contributing to the protection of patients' and public health.

Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging). Although some principles in this chapter apply to all types of safety communication; including addressing public concerns and safety crisis, the chapter itself focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicine which has or could have an impact on a medicine's risk-benefit balance and its condition of use.

Communication of important new safety information on pharmaceutical products shall take into account the views and expectations of concerned parties, including patients and healthcare professionals, with due consideration given to relevant legislation.

10.2. Structures and processes

10.2.1. Objectives of safety communication

Safety communication aims at:

- Providing timely, evidence-based information on the safe and effective use of medicines;
- Facilitating changes to healthcare practices (including self-medication practices) where necessary;
- Changing attitudes, decisions and behaviors in relation to the use of medicines;
- supporting risk minimization behavior;
- Facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high-quality safety communication can support public confidence in the regulatory system.

10.2.2. Principles of safety communication

The following principles of safety communication shall be applied:

- Safety communication shall deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
- Safety communication shall be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different

levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.

- The need for communicating safety information shall be considered throughout the pharmacovigilance and risk management process, and shall be part of the risk assessment and risk minimization measures.
- There shall be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. EDA, other public bodies and marketing authorization holders).
- Information on risks shall be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and expected time to recovery.
- Safety communication shall address the uncertainties related to a safety concern. This is of particular relevance for new information which is often communicated while EDA are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.
- Information on competing risks such as the risk of non-treatment shall be included where appropriate.
- The most appropriate quantitative measures shall be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; when comparing risks, denominators shall be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be considered to ensure it is clear and understandable by stakeholders.
- Patients, healthcare professionals and any concerned stakeholders shall, where possible, be consulted and messages pretested early in the preparation of safety communication, particularly on complex safety concerns.
- Where relevant safety communication shall be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
- The effectiveness of safety communication shall be evaluated where appropriate and possible (see 10.2.6.).
- Safety communications shall comply with relevant requirements relating to individual data protection and confidentiality.

10.2.3. Target audiences

The primary target audiences for safety communication issued by EDA and marketing authorization holders shall be patients, carers and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) pharmaceutical products.

As primary target audiences, healthcare professionals play an essential role in ensuring that medicines are used as effectively and safely as possible. Effective safety communication enables them to take adequate actions to minimize risks and to give clear and useful information to their patients during routine consultation as well as in case of a crisis event. This ultimately promotes patient safety and confidence in the regulatory system. Both healthcare professionals in clinical

practice and those involved in clinical trials shall be provided with appropriate information on any safety concern at the same time.

Patient, consumer and healthcare professional organizations can play a role as multipliers as they can disseminate important safety information to target audiences.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from EDA in addition to the information they receive from other sources.

10.2.4. Content of safety communication

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information shall not include any material or statement which might constitute advertising.

Therefore, taking into account the above provisions and the principles in 10.2.2., safety communication shall contain:

- Important new information or reminder about important information on any authorized pharmaceutical product which has an impact on the medicine's risk-benefit balance under any conditions of use;
- The reason for initiating safety communication clearly explained to the target audience;
- Any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- When applicable, a statement on the agreement between the marketing authorization holder and EDA on the safety information provided;
- Information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
- Any additional information about the use of the medicine or other data that may be relevant for tailoring the message to the targeted audience;
- A list of literature and website references, when relevant or a reference to where more detailed information can be found, and any other background information considered relevant;
- Where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

10.2.5. Means of safety communication

Communication tools and channels have become more numerous and varied over time, offering the public more information than was previously possible. Relevant communication tools and channels shall be considered when issuing a safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below in 10.2.5.1. to 10.2.5.9.

10.2.5.1. Direct healthcare professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorization holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a pharmaceutical product. DHPCs are not replies to enquiries from healthcare professionals.

The preparation of DHPCs involves cooperation between the marketing authorization holder and EDA. Agreement between these two parties shall be reached before a DHPC is issued by the marketing authorization holder. The agreement will cover both the content of the DHPC (see 10.٢،٤.) and the communication plan, including the intended recipients, the timetable and the channels for disseminating the DHPC.

Where there are several marketing authorization holders of the same active substance and/or a class of products for which a DHPC is to be issued, a single consistent message shall be delivered (see 10.3.2.1.).

A DHPC shall be complemented by other communication tools and channels and the principle of providing consistent information shall apply (10.2.2.).

A DHPC shall be included as an additional risk minimization measure as part of a risk management plan (see chapter 5).

A DHPC shall be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a pharmaceutical product:

- Suspension, withdrawal or revocation of a marketing authorization for safety reasons;
- An important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
- A restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.

Other situations where dissemination of a DHPC shall be considered are:

- New major warnings or precautions for use in the product information;
- New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- New evidence that the pharmaceutical product is not as effective as previously considered;
- New recommendations for preventing or treating adverse reactions or to avoid misuse or medication errors with the pharmaceutical product;
- Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC shall encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimize the potential risk).

EDA may disseminate or request the marketing authorization holder to disseminate a DHPC in any situation where EDA considers it necessary for the continued safe and effective use of a pharmaceutical product.

10.2.5.2. Communication materials from EDA targeted at healthcare professionals

EDA can issue safety communications targeting healthcare professionals directly.

These are usually published on the website of EDA (www.edaegypt.gov.eg) Here. These communications often complement other means for communicating a safety concern (e.g. a DHPC) and are issued around the same time. They contain EDA`s recommendations and advice for risk minimization for healthcare professionals, and provide relevant background information. Adequate links to further information can be included (e.g. links to the product information of the concerned pharmaceutical product(s) and, whenever possible, prescription and dispensing systems).

Safety communications from EDA shall follow the principles identified above (see 10.2.2.) and shall be issued when there is a need to take immediate action or change current practice in relation to a pharmaceutical product (see 10.2.5.1.) EDA shall also consider existing public interest when issuing a safety communication.

EDA shall make use of the most appropriate tools and channels described in this Section to maximize dissemination and accessibility of relevant information. This includes interaction with other organizations such as learned societies, local health facilities, patient and other healthcare organizations, as appropriate.

10.2.5.3. Documents in lay language to patients and the general public

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. It can also be an additional tool that healthcare professionals can use in their communication with patients. Lay language documents shall contain EDA's recommendations and advice for risk minimization for patients, and shall be accompanied by relevant background information.

Lay language documents shall be useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference shall be made to other communication materials on the topic to direct readers to where they can find further information.

For the dissemination and accessibility of lay language documents, the most appropriate tools and channels described in this Section shall be used as appropriate.

10.2.5.4. Press communication

Press communication includes press releases and press briefings which are primarily intended for journalists.

EDA may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with EDA`s scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Press releases may also be prepared and published by marketing authorization holders. Their press releases shall make reference to the regulatory action taken by EDA. Relevant ongoing reviews shall be mentioned in any communication by the marketing authorization holder.

10.2.5.5. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on pharmaceutical products. EDA as well

as marketing authorization holders shall ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites shall be kept up-to-date, with any information that is out-of-date marked as such or removed.

10.2.5.6. Social media and other online communications

Online safety information may also be disseminated via social media and other web tools. When using newer, more rapid communication channels, special attention shall be paid to ensure that the accuracy of the information released is not compromised. Communication practices shall take into account emerging digital communication tools used by the various target audiences.

10.2.5.7. Newsletters

Newsletters provide at regular intervals information about medicines and their safety and effectiveness. This tool may serve as reminders of previous communications. EDA can reach a large audience with this tool by using web-based and other available means. Here

10.2.5.8. Inter-authority communication

When one competent authority takes regulatory action on a particular safety concern, other authorities may also receive enquiries or may want to communicate on the same issue. The use of inter-authority communication material, such as lines-to-take shall be considered. Lines-to-take are documents prepared by a competent authority to assist its staff and those of co-operating authorities in responding consistently to external enquires or communicating a consistent message on a specific issue.

10.2.5.9. Responding to enquiries from the public

EDA and marketing authorization holders shall have systems in place for responding to enquiries about medicines from individual members of the public. Responses shall take into account the information which is in the public domain and shall include the relevant recommendations to patients and healthcare professionals issued by EDA. Where questions relate to individual treatment advice, the patient shall be advised to contact a healthcare professional.

10.2.5.10. Other means of communication

In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

Some tools and channels may be used in the context of risk management; in addition to the product information, other communication tools can be used to disseminate information about the product.

These are considered as additional risk minimization measures and may include patient alert cards or educational materials. These are outside the scope of this chapter and are described in more detail in chapter 12.

10.2.6. Effectiveness of safety communication

Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Where possible, mechanisms shall be introduced in order to measure the

effectiveness of the communication. A research-based approach will normally be appropriate in order to establish that safety communications have met the standard of 10.2.2. This approach may measure different outcomes, including behavior, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication (see Chapter 12).

In the case of DHPCs, marketing authorization holders shall inform EDA about the number of healthcare professionals who received the DHPC and about any difficulty identified during the dissemination of the DHPCs (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action shall be taken as needed to correct the situation or prevent similar problems in the future.

10.2.7. Quality system requirements for safety communication

In accordance with the quality system requirements in Chapter 1, procedures shall be in place to ensure that safety communications comply with the principles in 10.2.2. as appropriate.

In particular, safety communications shall be subject to quality controls to ensure their accuracy and clarity. For this purpose, review procedures with allocated responsibilities shall be followed and documented.

10.3. Operation in Egypt

10.3.1. Sharing of safety announcements in Egypt

In Egypt, patients and healthcare professionals increasingly look at EDA as providers of important information on medicines. For safety communication to be effective, adequate coordination and cooperation is required. A good level of coordination of safety communication is of particular importance so that healthcare professionals and patients receive consistent information on regulatory decisions in Egypt.

When issuing safety announcements, EDA may make use of the different tools and channels described in 10.2.5.

It is recommended that safety announcements by EDA to be done in cooperation with the concerned marketing authorization holder(s). Whenever possible, it is recommended that EDA provide any safety announcement prior to its publication to the concerned marketing authorization holder(s) (except in urgent situation). Any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

As a complement to the coordination of safety announcements with marketing authorization holder(s), EDA shall interact with concerned stakeholders (mainly patients' and healthcare professionals' organizations), who can play a key role in reviewing and disseminating information to the end users (patients and healthcare professionals). It is recommended that EDA keep up-to-date contact details of relevant patients' and healthcare professionals' organizations.

EDA shall develop a safety communication plan that identifies the different means for communicating safety information with different stakeholder.

10.3.1.1. Requirements for the marketing authorization holder in the Egypt

As soon as a marketing authorization holder in Egypt intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a pharmaceutical product, and in any event at the same time or before the public announcement is made, the marketing authorization holder shall be required to inform EDA.

Informing EDA at the same time as the public (i.e. without advance notice to EDA) shall only occur exceptionally and under justified grounds.

The marketing authorization holder shall ensure that information to the public is presented objectively and is not misleading.

Whenever a marketing authorization holder becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of a pharmaceutical product authorized in Egypt, the marketing authorization holder shall inform EDA and make every effort to share the content of the communications with the it.

10.3.1.2. Consideration for third parties

Third parties (e.g. editors of scientific journals, learned societies, patients' organizations) are encouraged to inform EDA of any relevant new information on the safety of medicines authorized in Egypt and, if publication is planned, to share the information ahead of publication.

10.3.2. Processing of safety communications

10.3.2.1. Emerging safety issues

A safety issue considered by a marketing authorization holder to require urgent attention by EDA because of the potential major impact on the risk-benefit balance of the pharmaceutical product and/or on patients' or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Examples include; not restricted to:

- Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- Major safety issues identified through the spontaneous reporting system or publications in the scientific literature, which may lead to considering a contraindication, a restriction of use of a pharmaceutical product or its withdrawal from the market;
- Major safety-related regulatory actions outside Egypt, e.g. a restriction of use of a pharmaceutical product or its suspension.
- Major safety issues may be foreseen due to shortage or lack of supply of products or raw materials.

These events/observations, which may affect the risk-benefit balance of a pharmaceutical product, are not to be submitted as ICSRs. They shall be notified as Emerging Safety Issues in writing to the general administration for pharmaceutical vigilance (PVGA); this shall be done immediately (no later than 5 working days), once published or implemented in other regulatory authorities, in which the product is marketed.

The document shall indicate the points of concern and the actions proposed in relation to the marketing application/authorization for the concerned pharmaceutical product. Those safety issues shall also be analyzed in the relevant sections of the periodic safety update report of the authorized pharmaceutical product.

In the period between the approval of the pharmacovigilance part of marketing authorization application and the granting of the marketing authorization, information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the pharmaceutical product under evaluation may become available to the applicant. It is the responsibility of the applicant to ensure that this information is immediately submitted to EDA.

10.3.2.2. Direct healthcare professional communications (DHPCs) in Egypt

A direct healthcare professional communication (DHPC) (see 10.2.5.1.) is usually disseminated by one or a group of marketing authorization holders for the respective pharmaceutical product(s) or active substance(s), either at the request of EDA, or on the marketing authorization holder ‘s own initiative. The marketing authorization holder shall seek the agreement of EDA regarding the content of a DHPC (and communication plan) prior to dissemination.

Where there are several marketing authorization holders of the same active substance for which a DHPC is to be issued; a single consistent message shall normally be delivered.

- In case of DHPC published by reference regulatory authority; marketing authorization holders shall use the template published by the reference authority to ensure a single unified message being delivered by all MAHs.
- In case of DHPC initiated by General Administration for Pharmaceutical Vigilance, marketing authorization holders shall submit a proposed DHPC which will be assessed by the General Administration for Pharmaceutical Vigilance, and then a unified DHPC template will be issued to all MAHs to be used a reference template, ensuring a single unified message being delivered.

Timing of DHPC notification

Primary notification of Emerging safety issues and Direct Health Care Professional Communication (DHPC) immediately (no later than 5 working days) after being published or implemented in other regulatory authorities, in which the product is marketed.

The General Administration for Pharmaceutical Vigilance may disseminate (in special cases) or request the marketing authorization holder to disseminate a DHPC in any situation where EDA considers it necessary for the continued safe and effective use of a pharmaceutical product.

It is the responsibility of the applicant to ensure that this information is immediately submitted to the General Administration for Pharmaceutical Vigilance where the application is under assessment.

Processing of DHPCs

The situations when a DHPC is necessary or shall be considered are provided in 10.2.5.1. When drafting a DHPC, the template (see Annex III.5) and the guidance provided in the annotations in the
template shall be followed as appropriate.
The marketing authorization holder shall submit the following:

- draft DHPC; and
- **the dissemination list** also known as ―intended recipient list: the intended recipients HCPs groups may be general practitioners, specialists, pharmacists, nurses; hospitals/ambulatory care/other institutions as appropriate. The list shall specify the intended recipients name, specialty, contact information and geographical distribution; When defining the target groups of recipients, it shall be recognized that it is not only important to communicate with those HCPs who will be able or likely to prescribe or administer the pharmaceutical product, but also to those who may diagnose adverse reactions, e.g. emergency units, poison centers, or to appropriate specialists, e.g. cardiologists. It is also important to consider provision of DHPCs to relevant pharmacists (hospital and /or community) who serve as information providers within healthcare systems and provide assistance and information to Patients, HCPs, including hospital wards and poison centers, as well as the general public.
- **timetable for disseminating** the DHPC: the proposed timetable shall be appropriate according to the urgency of the safety concern.
- **dissemination mechanism**: how the DHPC is planned to be disseminated, the proposed mechanism shall be selected appropriately to meet the dissemination timetable.

The last 3 items above are known as the communication plan.

The marketing authorization holder shall submit these documents in the form of one full original one soft copy, after approval by EDA; the MAH will receive back the hard copy stamped with ‖approved‖, while the soft copy will be retained at the authority.
The marketing authorization holder shall allow a minimum of two working days for comments. However, whenever possible more time shall be allowed. The timing may be adapted according to the urgency of the situation. EDA will review the DHPCs (may request advice from its scientific committees/ national pharmacovigilance committee as appropriate.
Once the content of a DHPC and communication plan from the MAH are agreed by EDA, the MAH can start dissemination of the agreed DHPC (i.e. the MAH shall NOT start disseminating the DHPC prior to obtaining the approval from EDA).
The marketing authorization holder(s) shall adhere to the Communication Plan agreed with EDA.

Any significant event or problem occurring during the DHPC dissemination which reveals a need to change the Communication Plan or a need for further communication to Healthcare Professionals, this shall be notified in a timely manner to EDA to be approved.
After dissemination of a DHPC, a closing review shall be performed by the MAH, a progress report may be submitted upon request of EDA.
In cases where a medicines authority in other country requests the dissemination of a DHPC in its territory, the marketing authorization holder shall notify EDA.

This is in the context of the national legal requirement under which the marketing authorization holder shall notify EDA of any new information which may impact the benefit-risk balance of a pharmaceutical product. The need for any subsequent communication, e.g. a DHPC shall be considered and agreed on a case-by- case basis.

A flow chart describing the processing of DHPCs is provided in Annex IV at the end of the Chapter.

10.3.2.3. Translation of safety communications

The usual language for preparing safety communications and DHPCs will be English (unless other language is requested by the medicines authority).

Consult with EDA for requirements.

10.3.2.4. Publication of safety communications

EDA may publish safety communications and DHPCs on its official website. The timing for such publication shall be aligned to that of the dissemination of DHPC. EDA may also issue an additional safety announcement, and disseminate the DHPC to relevant healthcare professionals ‘organizations as appropriate.

11. Additional monitoring

11.1. Introduction

Pharmacovigilance is a vital public health function with the aim of rapidly detecting and responding to potential safety hazards associated with the use of pharmaceutical products.

A pharmaceutical product is authorized on the basis that; its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication (s). However, not all risks can be identified at the time of initial authorization and some of the risks associated with the use of a pharmaceutical product emerge or are further characterized in the post-authorization phase of the product 's lifecycle. To strengthen the safety monitoring of pharmaceutical products, this guideline has introduced a framework for enhanced risk proportionate post-authorization data collection for pharmaceutical products, including the concept of additional monitoring for certain pharmaceutical products.

These pharmaceutical products will be readily identifiable by an inverted equilateral black

triangle. ▼

That triangle will be followed by an explanatory statement in the summary of product characteristics (SmPC) as follows:

"This pharmaceutical product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section ..... for how to report adverse reactions."

A similar statement will also be included in the package leaflet. This explanatory statement shall encourage healthcare professionals and patients to report all suspected adverse reactions.

Post-authorization spontaneous Adverse Drug Reactions (ADR) reports remain a cornerstone of pharmacovigilance. Data from ADR reports is a key source of information for signal detection activities. Increasing the awareness of healthcare professionals and patients of the need to report suspected adverse drug reactions and encouraging their reporting is therefore an important means of monitoring the safety profile of a pharmaceutical product.

The concept of additional monitoring originates primarily from the need to enhance the ADR reporting rates for newly authorized products for which the safety profile might not be fully characterized or for products with newly emerging safety concerns that also need to be better characterized. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of pharmaceutical products.

This Chapter is divided in two sections:

- 11.2. provides general principles for assigning additional monitoring status to pharmaceutical products and on communication and transparency aspects.
- 11.3. describes the operation in Egypt regarding the supervision of additional

monitoring status, the communication strategy and the impact on pharmacovigilance activities.

11.2. Structures and processes

11.2.1. Principles for assigning additional monitoring status to a pharmaceutical product

All medicines are authorized on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorization, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from those in everyday medical practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. Marketing authorization holders and EDA, continuously monitor pharmaceutical products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the pharmaceutical product. However, for certain pharmaceutical products enhanced post-authorization data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain pharmaceutical products and in particular to encourage the spontaneous reporting of ADRs, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a pharmaceutical product at the time of granting a marketing authorization or in some cases at later stages of the product life cycle for a pharmaceutical product for which a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorization for pharmaceutical products containing a new active substance and for all biological pharmaceutical products, which are priorities for pharmacovigilance. EDA may also require additional monitoring status for a pharmaceutical product which is subject to specific obligations e.g. the conduct of a Post-Authorization Safety Study (PASS) or restrictions with regards to the safe and effective use of the pharmaceutical product.

11.2.2. Communication and transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. This can be achieved for example by highlighting the need to better characterize the safety profile of a new pharmaceutical product by identifying additional risks but placing those potential risks in the context of the known benefits for this product. A publicly available list of pharmaceutical products with additional monitoring status is kept up to date by the European Medicines Agency. In addition, healthcare professionals and patients shall be enabled to easily identify those products through their product labelling.

11.3. Operation in Egypt

11.3.1. Criteria for including a pharmaceutical product in the additional monitoring list

11.3.1.1. Mandatory scope

It is mandatory to include the following categories of pharmaceutical products in the list:

- Pharmaceutical products that contain a new active substance which, on 1 July 2015, was not contained in any innovative pharmaceutical product;
- Any biological pharmaceutical product not covered by the previous category and authorized after 1 July 2015;
- Products for which a PASS was requested at the time of marketing authorization
- Products authorized with specific obligations on the recording or suspected adverse drug reactions
- Products for which a PASS was requested following the grant of marketing authorization
- Products which were granted a conditional marketing authorization
- Products authorized under exceptional circumstances. (Exceptional circumstances is a type of marketing authorization granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical)

11.3.1.2. Optional scope

EDA has the right to impose additional monitoring activities to certain products, not falling under the mandatory scope, according to special situation which are:

- When a marketing authorization is granted subject to one or more of the following:
  - Conditions or restrictions with regard to the safe and effective use of the pharmaceutical product
  - Measures for ensuring the safe use of the pharmaceutical product to be included in the risk management system;
  - An obligation to conduct a post-authorization efficacy study;
  - The existence of an adequate pharmacovigilance system;

The scope of the above does not only include pharmaceutical products which are authorized or for which conditions are established in Egypt after becoming into effect the new "Good Pharmacovigilance Practice in Egypt" but also pharmaceutical products which were authorized or made subject to conditions before such date, provided they fall within one or more of the above situations for the optional scope.

Pharmacovigilance rules in general and additional monitoring specifically take into account that

the full safety profile of pharmaceutical products can only be confirmed after products have been placed on the market. Due consideration shall, therefore, be given to the merit of inclusion of a pharmaceutical product in the list in terms of increasing awareness about the safe and effective use of a pharmaceutical product and/or providing any additional information for the evaluation of the product. In this regard, the decision to include a pharmaceutical product subject to conditions in the list shall take account of the nature and scope of the conditions or obligations placed on the marketing authorization including their potential public health impact. The decision shall also consider the usefulness of the additional monitoring status in relation to other additional pharmacovigilance activities proposed in the risk management plan, for example in relation to the objectives of PASS.

11.3.2. Criteria for defining the initial time period of maintenance in the additional monitoring list

11.3.2.1. Mandatory scope

For pharmaceutical products containing new active substances as well as for all biological pharmaceutical products approved after 1 July 2015, the initial period of time for inclusion is five years after the marketing authorization date.

11.3.2.2. Optional scope

The period of time for inclusion in the list of pharmaceutical products authorized subject to conditions is decided by EDA, and it is linked to the fulfilment of the conditions and obligations placed on the marketing authorization.

If new conditions are imposed to the marketing authorization during a product ‘s lifecycle, it is envisaged that a pharmaceutical product previously removed from the EU list can be subjected to additional monitoring again if criteria for inclusion are met.

11.3.3. Roles and responsibilities

11.3.3.1. EDA

- EDA relies on the EU List of medicinal products under additional monitoring
- that is publicly available, created and maintained by the European Medicines Agency
- EDA can possibly decide which authorized pharmaceutical product shall be subject to additional monitoring (see 11.3.1.2)

11.3.3.2. The Marketing authorization holder

The marketing authorization holder:

- Shall include in the SmPC and Package leaflet of their pharmaceutical products subject to additional monitoring the black triangle symbol ▼ and the standardized explanatory statement on additional monitoring;
- Shall include information on the status of additional monitoring in any material to be

distributed to healthcare professionals and patients and shall make all efforts to encourage reporting of adverse reactions, as agreed with EDA:

- Shall provide evidence to EDA concerned on the status of any conditions imposed by them;
- Shall submit the relevant variation to include/remove the black symbol, the statement, and the standardized explanatory sentence from the SmPC and PL, where applicable.

11.3.4. Black symbol and explanatory statements

For pharmaceutical products included in the list, the SmPC shall include the statement:

"This pharmaceutical product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section ..... for how to report adverse reactions.",

Preceded by an inverted equilateral black triangle. A similar statement will also be included in the package leaflet. Once the pharmaceutical product is included or removed from the list, the marketing authorization holder shall update the SmPC and the package leaflet to include or remove, as appropriate, the black symbol, the statement, and the standardized explanatory statement.

If the decision to include or remove a pharmaceutical product from the list is done during the assessment of a regulatory procedure (e.g. marketing authorization application, extension of indication, renewal) the SmPC and the package leaflet shall be updated before finalization of the procedure in order to include or remove the black triangle symbol and explanatory statement from the product information.

If the decision to include or remove a pharmaceutical product from the list is done outside a regulatory procedure, then the marketing authorization holder is requested to subsequently submit a variation to update the product information of that product accordingly.

12. Risk minimization measures: selection of tools and effectiveness indicators

12.1. Introduction

Risk minimization measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Planning and implementing risk minimization measures and assessing their effectiveness are key elements of risk management.

The guidance provided in this Chapter shall be considered in the context of the wider GVP guidance, in particular in conjunction with Chapter "Risk Management Systems".

Risk minimization measures may consist of routine risk minimization or additional risk minimization measures. Routine risk minimization is applicable to all pharmaceutical products, and involves the use of the following tools, which are described in detail in Chapter "Risk Management Systems":

- The summary of product characteristics (SmPC);
- The package leaflet;
- The labelling;
- The pack size and design;
- The legal (prescription) status of the product.

Additional risk minimization measures are described in detail in this Chapter.
Therefore, both Chapters have to be read together for a full understanding of the selection of risk minimization tools.
Safety concerns of a pharmaceutical product are normally adequately addressed by routine risk minimization measures (see Chapter "Risk Management Systems"). In exceptional cases however, routine risk minimization measures will not be sufficient for some risks and additional risk minimization measures will be necessary to manage the risk and/or improve the risk-benefit balance of a pharmaceutical product. This chapter provides particular guidance on the use of additional risk minimization measures, including the selection of tools and the evaluation of their effectiveness. In specific circumstances, however, the effectiveness evaluation may also apply to routine risk minimization measures associated with safety concern(s) which are described in the SmPC/PIL (e.g. the SmPC provides guidance for clinical actions beyond routine standards of clinical care for either the risk itself or management of the target population), In these circumstances, the guidance provided in this Chapter on effectiveness evaluation also applies to routine risk minimization measures.

On the basis of the safety concerns described in the safety specification, the appropriate risk minimization measures shall be determined. Each safety concern needs to be individually considered and the selection of the most suitable risk minimization measure shall take into account the seriousness of the potential adverse reaction(s) and its severity (impact on patient), its preventability or the clinical actions required to mitigate the risk, the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety

concern may be addressed using more than one risk minimization measure, and a risk minimization measure may address more than one safety concern.

The marketing authorization holder shall include all risk minimization measures in the risk management plan and monitor their outcome.

This Chapter provides guidance on the principles for:

- The development and implementation of additional risk minimization measures, including examples of risk minimization tools;
- The evaluation of the effectiveness of risk minimization measures.

Part 12.2. describes the development, implementation and co-ordination of risk minimization measures and the general principles of the evaluation of their effectiveness.

Part 12.3. considers the application of those measures and principles in the setting of EDA regulations in Egypt.

12.2. Structures and processes

12.2.1. General Principles

Risk minimization measures aim to optimize the safe and effective use of a pharmaceutical product throughout its life cycle. The risk-benefit balance of a pharmaceutical product can be improved by reducing the burden of adverse reactions or by optimizing benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). Risk minimization measures shall therefore guide optimal use of a pharmaceutical product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.

The majority of safety concerns are addressed by routine risk minimization measures. Exceptionally, for selected important risks, routine risk minimization may be considered insufficient and additional risk minimization measures may be deemed to be necessary. In determining if additional risk minimization activities are needed, safety concerns shall be prioritized in terms of frequency, seriousness, severity, impact on public health and preventability. Careful consideration shall then be given to whether the goal can be reached with routine minimization activities, and, if not considered sufficient, which additional minimization measure(s) is (are) the most appropriate. Additional risk minimization measures shall focus on the most important, preventable risks and the burden of imposing additional risk minimization shall be balanced with the benefit for patients.

A variety of tools are currently available for additional risk minimization. This field is continuously developing, and new tools are likely to be developed in the future. Technology advances, such as interactive web-based tools may gain prominence in the future in addition to the paper-based educational materials.

Successful implementation of additional risk minimization measures requires contributions from all impacted stakeholders, including marketing authorization applicants or holders, patients and healthcare professionals. The performance of these measures in healthcare systems requires

assessment to ensure that their objectives are fulfilled and that the measures in place are proportionate taking account of the risk-benefit balance of the product and the efforts required of healthcare professionals and patients to implement the measures. It is therefore important to ensure that additional risk minimization measures, including assessment of their effectiveness, do not introduce undue burden on the healthcare delivery system, the marketing authorization holders, the regulators, and, most importantly, on the patients. To this aim, they shall have a clearly defined objective relevant to the minimization of specific risks and/or optimization of the risk-benefit balance. Clear objectives and defined measures of success with milestones need to guide the development of additional risk minimization measures and close monitoring of both their implementation and ultimate effectiveness is necessary. The nature of the safety concern in the context of the risk-benefit balance of the product, the therapeutic need for the product, the target population and the required clinical actions for risk minimization are factors to be considered when selecting risk minimization tools and an implementation strategy to accomplish the desired public health outcome. The evaluation of effectiveness shall facilitate early corrective actions if needed and may require modification over time. It is recognized that this is an evolving area of medical sciences with no universally agreed standards and approaches. Therefore, it is important to take advantage of any relevant elements of methodology from Pharmacoepidemiology and other disciplines, such as social/behavioral sciences and qualitative research methods.

The introduction of additional risk minimization shall be considered as a "programme" where specific tools, together with an implementation scheme and evaluation strategy are developed. The description of risk minimization measures, an integral part of the RMP, shall therefore give appropriate consideration to the following points:

- **Rationale**: When additional risk minimization measure(s) are introduced a rationale shall be provided for those additional measures;
- **Objectives**: Each proposed additional risk minimization measure(s) shall include defined objective(s) and a clear description of how and which safety concern is addressed with the proposed additional risk minimization measure(s);
- **Description**: This section of the RMP shall describe the selected additional risk minimization measures, including tools that will be used and key elements of content;
- **Implementation**: This section of the RMP shall provide a detailed proposal for the implementation of additional risk minimization measures (e.g. setting and timing or frequency of intervention, details of the target audience, plan for the distribution of educational tools; how the action will be coordinated where more than one marketing authorization holder is involved);
- **Evaluation**: This section of the RMP shall provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimization measures in process terms and in terms of overall health outcome measures (e.g. reduction of risk).

12.2.2. Risk minimization measures

Risk minimization measures aim to facilitate informed decision making to support risk minimization when prescribing, supplying and/or using a pharmaceutical product. While routine measures are applied to every pharmaceutical product (see details in Chapter "Risk Management

Systems") additional risk minimization activities shall only be introduced when they are deemed to be essential for the safe and effective use of the pharmaceutical product and shall be developed and provided by suitably qualified people.

Additional risk minimization measures may differ widely in purpose, design, target audience and complexity. These measures might be used to guide appropriate patient selection with the exclusion of patients where use is contraindicated, to support on-treatment monitoring relevant to important risks and/or management of an adverse reaction once detected. Additionally, specific measures may be developed to minimize the risk of medication error and/or to ensure appropriate administration of the product where it is not feasible to achieve this through the product information and labelling alone.

Section 12.2.2. describes additional risk minimization measures that may be considered in addition to the routine measures, including:

- Educational programs;
- Controlled access programs;
- Other risk minimization measures.

12.2.2.1. Educational programme

Educational programmes are based on targeted communication with the aim to supplement the information in the summary product characteristics (SmPC) and package leaflet. Any educational material shall focus on actionable goals and shall provide clear and concise messages describing actions to be taken in order to prevent and minimize selected safety concerns.

The aim of an educational programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimizing risk. Educational materials shall therefore be built on the premise that there is an actionable recommendation for targeted education and that applying this measure is considered essential for minimizing an important risk and/or for optimization of the risk-benefit balance. In the context of an educational programme, the tools can have several different target audiences, can address more than one safety concern and can be delivered using a combination of tools and media (e.g. paper, audio, video, web, in-person training). Ideally, educational materials shall be available in a range of formats so as to ensure that access is not limited by disability or access to the internet. When feasible the appropriateness of the tool and media for the target audience (e.g. suitable language, pictures, diagrams, or other graphical support) shall be user tested in advance, in order to optimize the success of the implementation phase.

The content of any educational material shall be fully aligned with the currently approved product information for a pharmaceutical product, such as the SmPC and package leaflet, and shall add rather than duplicate SmPC and package leaflet information. Promotional elements, either direct or veiled (e.g. logos, product brand colors, suggestive images and pictures), shall not be included and the focus of the educational material shall be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimization.

Any educational programme shall be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes shall not be used for promotional activities.

The educational tools described below can be considered individually or in combinations while

developing an educational programme for the purpose of additional risk minimization.

Educational tools

An educational tool shall have a clearly defined scope and shall include unambiguous statement(s) regarding the important risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s) and the specific steps to be taken by healthcare professionals and/or patients in order to minimize those risks. This information shall focus on clearly defined actions related to specific safety concerns described in the RMP and shall not be unnecessarily diluted by including information that is not immediately relevant to the safety concern and that is adequately presented in the SmPC or package leaflet. Educational tools shall refer the reader to the SmPC and the package leaflet. In addition to an introductory statement that the educational material is essential to ensure the safe and effective use and appropriately manage important selected risks, elements for inclusion in an educational tool could provide:

- Guidance on prescribing, including patient selection, testing and monitoring;
- Guidance on the management of such risks (to healthcare professionals and patients or carers);
- Guidance on how and where to report adverse reaction of special interest.

Educational tools targeting healthcare professionals

The aim of any educational tool targeting a healthcare professional shall be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage adverse reactions) associated with the medicine and the specific important risks needing additional risk minimization measures, including:

- Selection of patients;
- Treatment management such as dosage, testing and monitoring;
- Special administration procedures, or the dispensing of a pharmaceutical product;
- Details of information which needs to be given to patients.

The format of a particular tool will depend upon the message to be delivered. For example, where a number of actions are needed before writing a prescription for an individual patient, a checklist may be the most suitable format. A brochure may be more appropriate to enhance awareness of specific important risks with a focus on the early recognition and management of adverse reactions, while posters for display in certain clinical environments can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the scope of the tool.

Educational tools targeting patients and/or carers

The aim of tools targeting patients shall be to enhance the awareness of patients or their carers on the early signs and symptoms of specific adverse reactions causing the need for additional risk minimization measures and on the best course of action to be taken shall any of those symptoms occur. If appropriate, a patient ‘s educational tool could be used to provide information on the correct administration of the product and to remind the patient about an important activity,

for example a diary for posology or diagnostic procedures that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to.

Patient alert card

The aim of this tool shall be to ensure that special information regarding the patient ‘s current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information shall be kept to the minimum necessary to convey the key minimization message(s) and the required mitigating action, in any circumstances, including emergency. Ability to carry with ease (e.g. can be fitted in a wallet) shall be a key feature of this tool.

12.2.2.2. Controlled access programme

A controlled access programme consists of interventions seeking to control access to a pharmaceutical product beyond the level of control ensured by routine risk minimization measures i.e. legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme shall be limited and shall be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is life- threatening), and whether this risk is expected to be managed by the interventions. Therefore, controlled access shall only be considered as a tool for minimizing an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination):

- Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
- Prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product;
- Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry;
- Medicines made available for dispensing only by Pharmacies which are registered and approved to dispense the product.

On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example, monitoring of the patient ‘s health status, laboratory values or other characteristic prior to and/or during treatment, e.g. ECG, liver function tests, regular blood tests, pregnancy test (which can be part of a pregnancy prevention programme). Measures shall be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

12.2.2.3. Other risk minimization measures

Controlled distribution systems

A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a pharmaceutical product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in Egypt under the respective EDA legislations to prevent misuse and abuse of medicines.

Pregnancy prevention program

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimize pregnancy exposure during treatment with a pharmaceutical product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a pharmaceutical product by the biological father might have a negative effect on pregnancy outcome.

A PPP combines the use of educational tools with interventions to control appropriately access to the medicine. Therefore, the following elements shall be considered individually and/or in combination in the development of a PPP:

- Educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimize this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraception; information included for the patient on how long to avoid pregnancy after treatment is stopped; information for when the male partner is treated;
- Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the pharmaceutical product;
- Prescription limited to a maximum of 30 days supply;
- Counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

The design and implementation of a pregnancy registry (as a stand-alone activity or as part of a pregnancy prevention programme) shall also be considered for universal enrolment of patients who become pregnant during treatment or within an appropriate time from the end of treatment e.g. 3 months. Use of this systematic tool to collect pregnancy outcome information can be helpful in assessing the effectiveness of the pregnancy prevention programme and/or in facilitating further characterization of the risk, particularly in the early period post authorization when human pregnancy data may be very limited and/or when the potential concern may be based on non-clinical data alone.

Direct health care professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorization holder or by the authority, to inform them of the need to take certain actions or adapt their practices in relation to a pharmaceutical product. For example, a DHPC may aim at

adapting prescribing behavior to minimize particular risks and/or to reduce the burden of adverse reactions with a pharmaceutical product.

12.2.3. Implementation of risk minimization measures

Additional risk minimization measures can consist of one or more interventions that shall be implemented in a sustainable way in a defined target group. Careful consideration shall be given to both the timing and frequency of any intervention and the procedures to reach the target population. For example, a one-off distribution of educational tools may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached. Additional periodic redistribution of the tools might be necessary. Conversely, educational materials required at the time of launch of a new pharmaceutical product may no longer be necessary or relevant once it has been available for a number of years. Because risk minimization measures serve different purposes, some measures such as alert cards, controlled access programs and pregnancy prevention programs, will usually apply to all future applications for the same pharmaceutical product, whilst others, such as DHPCs and training materials, may not necessarily be needed for all future applications. The appropriateness of each measure and whether these will be required for the future applications for the same pharmaceutical products shall be carefully considered at the time of authorization of the product (and made clear in the RMP). Careful consideration shall be given to the layout and content of the educational tools to ensure a clear distinction from any promotional material distributed. Submission of educational material for review by EDA shall be separate from submission of promotional material and a cover letter shall clearly state whether the materials are promotional or educational.

Furthermore, educational tools shall be distributed separately from promotional materials as a ‘stand-alone ‘communication and it shall be clearly stated that the tools are not promotional material, but rather have risk minimization purposes.

Quality assurance mechanisms shall ensure that the distribution systems in place are fit for purpose and auditable.

12.2.4. Effectiveness of risk minimization measures

Evaluating the effectiveness of additional risk minimization measures is necessary to establish whether an intervention has been effective or not, and if not why and which corrective actions are necessary. The evaluation shall be performed for the additional risk minimization tools individually and for the risk minimization programme as a whole.

Effectiveness evaluation shall be conducted at the most appropriate time, accounting for time required for launch of the risk minimization measures, estimated use of the product by the healthcare system and other relevant circumstances.

Periodic review of the effectiveness of one or more specific tools or the overall programme, as appropriate shall be also planned. Time points of particular relevance are as follows:

- After initial implementation of a risk minimization programme (e.g. within 12-18 months), in order to allow the possibility of amendments, shall they be necessary;
- In time for the evaluation of the renewal of a marketing authorization;

whenever effectiveness is evaluated, careful consideration shall be given on the need for

continuing with the additional risk minimization measure.

Effectiveness evaluation shall address different aspects of the risk minimization, the process itself (i.e. to what extent the programme has been implemented as planned), its impact on knowledge and behavioral changes in the target audience (i.e. the measure(s) in affecting behavioral change), and the outcome (i.e. to what extent the predefined objectives of risk minimization were met, in the short and long term). In designing an evaluation strategy, due consideration needs to be made toward what aspects of process and outcomes can be realistically measured in order to avoid the generation of inaccurate or misleading data or placing an undue burden on the healthcare system or other stakeholders. The time of assessing each aspect of the intervention as well as setting of realistic metrics on which the effectiveness of the tool is judged, shall also be carefully considered and planned prior to initiation.

To evaluate the effectiveness of additional risk minimization measures two categories of indicators shall be considered:

- Process indicators;
- Outcome indicators.

Process indicators are necessary to gather evidence that the implementing steps of additional risk minimization measures have been successful. These process indicators shall provide insight into what extent the programme has been executed as planned and whether the intended impacts on behavior have been observed. Implementation metrics shall be identified in advance and tracked over time. The knowledge gained may be used to support corrective implementation action as needed. Assessing the implementation process can also improve understanding of the process(es) and causal mechanism(s) whereby the additional risk minimization measure(s) did or did not lead, to the desired control of specified important risks.

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

In rare circumstances when it is fully justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators.

The conclusion of the evaluation may be that risk minimization shall remain unchanged or modifications are to be made to existing activities. Alternatively, the assessment could indicate that risk minimization is insufficient and shall be strengthened (e.g. through amendment of warnings or recommendations in the SmPC or package leaflet, improving the clarity of the risk minimization advice and/or by adding additional tools or improving existing tools). Another decision may be that the risk minimization is disproportionate or lacking a clear focus and could be reduced or simplified (e.g. by decreasing the number of tools or frequency of intervention, or by eliminating interventions proved to be non-contributory to risk minimization). In all circumstances, the burden on the patient and the healthcare system shall be given careful consideration.

In addition to measuring the effectiveness of risk minimization measures in managing safety

concerns, it is also important to monitor if the risk minimization intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term. Examples of unintended consequences may include undue burden on the healthcare system, or discontinuation of a product even if its risk-benefit balance remains positive.

This guidance defines "Any study measuring the effectiveness of risk management measures" as a post-authorization safety study. Therefore, if a study is conducted to assess behavioral or safety outcome indicators the detailed guidance for conducting a post-authorization safety study, shall be followed. Such guidance does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population).

12.2.4.1. Process indicators

Process indicators are measures of the extent of implementation of the original plan, and/or variations in its delivery. Process indicators shall complement but not replace the assessment of the attainment of the objectives of the risk minimization measures (i.e. outcome indicators). Depending on the nature of the interventions various process indicators can be identified for the assessment of their performance.

Reaching the target population

When risk minimization measures involve the provision of information and guidance to healthcare professionals and/or patients by mean of educational tools, measures of distribution and receipt shall be used to acquire basic information on implementation. These metrics shall focus on assessing whether the materials were delivered to the target audience and whether they were actually received by the target population. (Example: progress reports)

Assessing clinical knowledge

In order to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (for example via an educational programme with a goal of preventing drug exposure during pregnancy), scientifically rigorous survey methods shall be applied.

A survey generally includes a set of standard questions administered through telephone contact, in person interview, or self-administered through postal/electronic communication, which are repeated over time. Such an approach may be tailored to the monitoring of attitude and knowledge in a diverse sample, that includes representatives from each segment of interest in the target populations of healthcare professionals and/or patients. Psychometric measures shall be used as appropriate. Whenever feasible a randomized sample and an adequate sample size shall be selected. In contrast, use of advocacy groups or patient support groups to survey knowledge can be considered to be inherently biased through self-selection, and shall be avoided.

Appropriate attention shall be given to the research objectives, study design, sample size and representativeness, operational definition of dependent and independent variables, and statistical analysis. Thorough consideration shall also be given to the choice of the most appropriate data collection instruments (e.g. questionnaires).

Assessing clinical actions

In order to evaluate the effectiveness of educational interventions and/or information provisions,

not only clinical knowledge but also the resulting clinical actions (i.e. prescribing behavior) shall be measured. Drug utilization studies by means of secondary use of electronic records or through medical chart abstraction are valuable options to quantify clinical actions, if representative of the target population and where adequate databases are accessible. The analysis of prescription records, especially when linked to other records of patients (e.g. clinical and demographic data), may allow the evaluation of prescribing behavior, including co-prescribing of two interacting pharmaceutical products, compliance with laboratory monitoring recommendations, as well as patient selection and monitoring. By applying appropriate statistical methods (e.g. time series analyses, survival analyses, logistic regression) to a cohort of medicines users, different aspects of prescribing or use may be assessed, which can provide insights beyond purely descriptive evidence.

Careful consideration shall be given to the conduct and interpretation of drug utilization studies in Egypt including the legal status of the medicine and how it is prescribed and dispensed, since prescription patterns may reflect not only the product information and any risk minimization intervention, but also EDA guidelines, aspects related to healthcare services, local medical practice, and reimbursement constraints.

The study of behavior based on data collected through surveys shall only be considered when no pre-existing data are available to evaluate clinical actions (i.e. conduct a drug utilization study based on self-reported data collected in healthcare professionals and/or patients survey).

12.2.4.2. Outcome indicators

The ultimate measures of success of a risk minimization programme are the safety outcomes, i.e. the frequency and/or severity of adverse reactions in relation to patients 'exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting) and those safety outcomes shall be the outcome indicator(s). Such an evaluation shall involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained for example in the context of post-authorization safety studies. The use of appropriate safety-related outcomes of interest shall be considered (e.g. a surrogate endpoint such as an adequate biomarker as a substitute for a clinical endpoint) if such an approach facilitates the effectiveness evaluation. Under any approach, scientific rigor and recognized principles of epidemiologic research shall always guide the assessment of the final outcome indicator of interest. Comparisons of frequency before and after the implementation of the risk minimization measures (i.e. pre-post design) shall be considered. When a pre-post design is unfeasible (e.g. risk minimization measures are put in place at the time of initial marketing authorization), the comparison of an outcome frequency indicator obtained post-intervention against a predefined reference value obtained from literature review, historical data, expected frequency in general population, would be acceptable (i.e. observed versus expected analysis) and shall take into account any stimulated reporting, changes in patient care and/or risk minimization measures over time. The selection of any particular reference group shall be appropriately justified.

Methods to measure the effectiveness of risk minimization measure shall be proportionate to the risks being minimized. As such use of spontaneous reporting rates (i.e. number of suspected adverse reaction reports over a fixed time period) may be acceptable in the context of routine

risk minimization. Spontaneous reporting shall be considered with caution when estimating the frequency of adverse events in the treated population, but it may be used in very specific circumstances, for instance when the adverse reaction with the product is rare and there is a negligible background incidence of the adverse event in the general population and a strong association between treatment and the adverse event. In those circumstances when a direct measure on the risk in the treated population is not feasible, spontaneous reporting could offer an approximation of the frequency of the adverse reaction in the treated population, provided that reasonably valid data can be obtained to evaluate the reporting rate in the context of product use.

However, the well know biases that affects reporting of suspected adverse reactions may provide misleading results. For instance, the introduction of a risk minimization measure in response to a safety concern detected in the post-authorization phase of a pharmaceutical product may raise awareness regarding related adverse reactions which ultimately may result in an increased reporting rate. In these circumstances an analysis of spontaneous reporting may lead to the erroneous conclusion that the intervention was ineffective. Decreasing reporting rates over time may also lead to the erroneous conclusion that the intervention was effective.

12.2.5. Coordination

If several products, referred to as ―generics of the same active substance are available in a market there shall be a consistent approach in the use of additional risk minimization measures coordinated and overseen by EDA. When a coordinated action for a class of products is needed a harmonized approach shall be agreed if appropriate. Under these circumstances advanced planning shall ensure that the effectiveness of risk minimization measures can be considered for each individual product as well as for the products collectively.

12.2.6. Quality systems of risk minimization measures

Although many experts may be involved in developing and implementing risk minimization measures, the final responsibility for the quality, accuracy and scientific integrity of those measures and the plan describing them lies with the marketing authorization holder and its qualified person responsible for pharmacovigilance (QPPV)/local safety responsible (LSR) in Egypt.

The marketing authorization holder is responsible for updating the RMP when new information becomes available and shall apply the quality principles. Tracked versions of the RMP shall be submitted to facilitate regulatory assessment. These records, the RMP and the associated risk management systems, as well as any documents on risk minimization measures may be subject to audit or inspection.

The marketing authorization holder shall ensure appropriate version control of the risk minimization tools in order to ensure that all healthcare professionals and patients receive up-to- date risk minimization tools in a timely manner and that the tools in circulation are consistent with the approved product information. To this purpose the marketing authorization holders are encouraged to keep track of the receipt of any risk minimization tools. These records may be subject to audit and inspection.

The marketing authorization holder shall ensure that mechanisms for reporting the results of studies or analyses for evaluation of the effectiveness of risk minimization measures are documented. These may be subject to audit or inspection.

12.3. Operation in Egypt

12.3.1. Roles and responsibilities in Egypt concerned for implementing additional risk minimization measures

Implementation of additional risk minimization measures shall take place at national level. EDA tailor the required conditions and restrictions to Egypt's legal requirements and healthcare systems.

12.3.1.1. Roles and responsibilities of EDA

EDA is responsible for the oversight of the implementation of all additional risk minimization measures for the safe and effective use of a pharmaceutical product in Egypt.

For those risk minimization measures introduced after the initial marketing authorization, EDA shall ensure prompt consideration and agreement of the interventions with the marketing authorization holder.

Additionally, EDA shall agree the final content, format and media of the risk minimization tools, including printed material, web-based platforms and other audio-video media, as well as the schedule planning of interventions with the applicant or marketing authorization holder before a product is introduced to their market or at any time thereafter as needed.

EDA is autonomous in deciding appropriate national educational materials and/or other risk minimization tools.

In addition to advising on the studies and measures described in the RMP, EDA may assess both protocol and results of imposed post-authorization safety studies which aim to evaluate the effectiveness of risk minimization measures.

EDA shall monitor the outcome of all risk minimization measures in Egypt. Hence, take as appropriate any necessary regulatory action

12.3.1.2. Marketing authorization applicant or holder

The applicant or marketing authorization holder shall clearly define the objectives of any proposed additional risk minimization measure and the indicators to assess their effectiveness. Any additional risk minimization intervention shall be developed in accordance with the general principles and shall be fully documented in the RMP (see chapter "Risk Management Systems").

The measures adopted in the RMP shall be implemented at national level after agreement with EDA.

The applicant or marketing authorization holder shall provide information regarding the status of implementation of additional risk minimization measures as agreed with EDA and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimization measures. Any relevant changes to the implementation of the tools shall be agreed with EDA before implementation.

In the implementation of web-based tools the applicant or marketing authorization holder shall apply requirements specific for the national level, with particular consideration of potential issues linked to accessibility, recognisability, responsibility, and privacy and data protection.

For generic products the applicant or marketing authorization holder shall develop risk minimization in line with the scope, content, and format of the tools used for the reference pharmaceutical product. Scheduling and planning of interventions shall be carefully coordinated in order to minimize the burden on the healthcare systems.

For generic products, the effectiveness of risk minimization measures shall be assessed by the marketing authorization holders in close co-operation with EDA Where formal studies are justified, joint studies for all pharmaceutical products involved are strongly encouraged in order to minimize the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry shall be independent from the prescription of a product with a specific invented name or marketing authorization holder. Recording of specific product details would still be important to enable rapid identification of any new safety hazard with a particular product.

The marketing authorization holder shall monitor the outcome of all risk minimization measures.

The applicant or marketing authorization holder shall report the evaluation of the impact of additional risk minimization activities when updating the RMP.

The applicant or marketing authorization holder shall report in the Periodic Benefit Risk Evaluation Report (PBRER) the results of the assessment of the effectiveness of risk minimization measures which might have an impact on the safety or risk-benefit assessment.

The applicant or marketing authorization holder shall ensure timely communication with EDA for relevant regulatory evaluation and actions, as appropriate.

12.3.1.3. Healthcare professionals and patients

Healthcare professionals and patients hold no legal obligations with respect to the implementation of the pharmacovigilance legislation. Nonetheless the cooperation of healthcare professionals and patients is paramount to the success of educational programs and/or controlled access programs in order to optimize the risk-benefit balance. It is desirable that they give careful consideration to any additional risk minimization measure which may be introduced for the safe and effective use of medicines.

12.3.2. Impact of risk minimization measures effectiveness on RMP/PBRER

PBRER and RMP updates shall include a summary evaluation of the outcome of specific risk minimization measures implemented to mitigate important risks in Egypt.

In the RMP, the focus shall be on how this informs risk minimization and/or pharmacovigilance planning.

In the PBRER, there shall also be evaluation of how the implemented measures impact on the safety profile and/or risk-benefit balance of the product. In general, the focus shall be on information which has emerged during the reporting period or since implementation of the most recent risk minimization measure(s) in Egypt. Where there is parallel submission of a PBRER and a RMP update, the use of a common content Chapter shall be considered.

Results of the assessment(s) of the effectiveness of risk minimization measures shall always be included in the RMP. As part of this critical evaluation, the marketing authorization holder shall make observations on factors contributing to the success or weakness of risk minimization measures. This critical analysis may include reference to experience in other countries worldwide, when relevant.

The evaluation of the effectiveness of risk minimization measures shall focus on whether these have succeeded in minimizing risk. This shall be analyzed using a combination of process and outcome indicators, It may be appropriate to distinguish between risk minimization measures implemented at the time of initial marketing authorization and those introduced later in the post-authorization phase.

When presenting the evaluation of the effectiveness of a risk minimization measure, the following aspects shall be considered:

- The evaluation shall provide context by
    a. briefly describing the implemented risk minimization measure(s),
    b. defining their objective(s), and
    c. outlining the selected process and outcome indicators.
- The evaluation shall incorporate relevant analyses of the nature of the adverse reaction(s) including its severity and preventability. Where appropriate logistical factors which may impact on clinical delivery of the risk minimization measure shall also be included.
- The evaluation shall include an examination of the delivery of the risk minimization measures in routine clinical practice, including any deviation from the original plan. Such an evaluation may include the results of drug utilization studies.
- Outcome indicators (i.e. adverse reaction frequency and/or severity; other safety-related outcomes) shall normally be the key endpoint when assessing the attainment of risk minimization measures objectives.

Proposals for changes to enhance risk management shall be presented in the national appendix of the PBRER. The RMP shall be updated to take account of emerging information on the effectiveness of risk minimization measures.

In general, the frequency of RMP updates shall be proportionate to the risks of the product. The focus of RMP updates shall be on the risk minimization measures and in providing updates on the implementation of those measures where applicable. If there is a consequential change to the summary RMP, this shall also be highlighted in the cover letter. Changes to the product information shall not be proposed via a standalone RMP update but rather a variation application shall be submitted. A PBRER can also result directly in an update to product information.

Appendix 1. Key elements of survey methodology

Surveys are systematic methods of collecting primary data directly from a sample of participants from a larger population. These are conducted in order to characterize the larger population and may be cross-sectional (one-time only) or longitudinal (repeated over time).

In the context of the evaluation of the effectiveness of risk minimization measures a survey can be conducted to evaluate understanding, knowledge and behavior resulting from educational interventions in a specified target population with respect to the safety and risk management of a pharmaceutical product.

The survey methodology might not be the most appropriate approach for the evaluation of behavior, since surveys collect and analyses self-reported data from healthcare professionals and patients. Furthermore, participation in a survey in itself may introduce behavior changes or may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals.

As a minimum, the following elements shall be considered in the design and implementation of a survey in order to minimize potential biases and to optimize the generalizability of the results to the intended population:

- Sampling procedures and recruitment strategy;
- Design and administration of the data collection instrument (s);
- Analytical approaches;
- Ethics, privacy, and overall feasibility of a study.

App1.1. Sampling procedures and recruitment strategy

In any survey, the sampling frame and recruitment of participants may be subject to selection bias leading to a study population that is not similar to, or representative of, the intended population in one or more aspects. Furthermore, it shall be considered that a bias cannot be eliminated only by increasing the sample frame, sample size and response rate. Bias can be minimized by selecting the optimal sampling frame, taking into account age, sex, geographical distribution and additional characteristics of the study population. Bias can also be minimized by assuring the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g., by oversampling a small but important subgroup). Key elements to be considered in the sampling frame include age, gender, geographical distribution, and additional characteristics of the study population. For example, in a physician survey, the strategy for randomly selecting the study sample shall consider whether a general random sample would be sufficient or if the sample shall be stratified by key characteristics such as specialty, type of practice (e.g., primary care, specialist ward, academic institution). In a patient survey, income and education, medical condition(s), chronic vs acute use, shall be considered.

In addition to the overall representativeness of the target population the recruitment strategy of a survey shall give careful consideration of the potential recruitment sources. For the recruitment of healthcare professionals, sponsor lists, web panels, professional and learned societies may represent feasible approaches. However, their representativeness for the intended target population of physicians needs to be carefully reviewed for each study. For patient recruitment the relevant clinical setting, existing web-panels, and patient advocacy groups shall be considered. A recruitment strategy shall be designed while accounting for the chances of achieving accurate and complete data collection.

Efforts shall be made to document the proportion of non-responders and their characteristics to evaluate potential influences on the representativeness of the sample.

App1.2. Design and administration of the data collection instrument(s)

Data collection approaches in a survey may vary from in-person interview, testing, and measurement or collection of biological samples as for routine clinical practice, to telephone interview, web-based or paper-based questionnaires. Audio computer-assisted self-interviewing (A-CASI), interactive voice response systems (IVRS), or mixed mode approaches may also be appropriate. The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics and the data to be collected.

Each data collection approach will require the ad hoc design of one or more specific instruments. Nonetheless general design considerations that may apply to all instruments include the following:

- Burden to participant: e.g. length or duration, cognitive burden, sensitivity to participant;
- Clarity and sequence of questions: e.g. use of unambiguous language, minimizing assumptions, starting with the most important questions and leaving sensitive questions until later;
- Completeness of responses: e.g. structure questions in order to lead to a single unambiguous answer, allow for choices such as ―unknown or ―don‘t know;
- Layout of data collection instrument: e.g. clear flow, technology-assisted guides (avoid patterns, reminders for non-response and visual images);
- Testing and revision of instrument: e.g. formal testing using cognitive pre-testing such as one-to- -one interviews, probing questions, interview guide or trained interviewer, and ―think aloud process;
- Incentives to improve response rate: e.g. fed back aggregated data to the survey participants.

App1.3. Analytical approaches

The key analytical elements of a survey shall include:

- Descriptive statistics, such as:
  - The percentage of participants responding correctly to knowledge questions;
  - Stratification by selected variable;
  - Data on no-response or incomplete response;
- Comparison of responders and non-responders’ characteristics (if data available);
- Comparison of responders and overall target population characteristics.

When survey results are weighted, the following key points shall be considered:

- Differences in selection probabilities (e.g. if certain subgroups were over-sampled);
- Differences in response rates;
- Post-stratification weighting to the external population;
- Clustering.

Examples of stratified analyses of physician ‘s survey include the following:

- Specialty of physician;

- Geographic location;
- Receipt of any educational material;
- Volume of prescribing.

App1.4. Ethics, privacy and overall study feasibility

There may be privacy considerations in allowing contact with physicians based on a prescriber list that is held by a pharmaceutical company.

The overall feasibility assessment of a study is a key step in the successful implementation of a survey. For clinical-based data collection, key elements of such an assessment include:

- Gathering information on site and characteristics of study population (patients or healthcare professionals);
- Estimating reasonable study sample size, the number of sites required to achieve the sample size, and approximate length of the data collection period (e.g. based on estimated patient volume, frequency of patient visits, and expected patient response rate);
- Evaluating site resources and interest in the study.

Key elements of a feasibility assessment may be different for other study designs (e.g. web-based recruitment and data collection) and for physician assessments.

13. Biological Products

13.1. Introduction

Biological products are products that contain one or more active ingredient produced or extracted from biological origin. For instance, they may include human vaccines, antisera, blood products and plasma derivatives, biotechnology-manufactured products and the like as well any products or materials that may be created according to science developments and/or international standards and references.

This Chapter applies to all biological pharmaceutical products regardless of the regulatory pathway of approval or market exclusivity status, i.e. it applies to reference biological pharmaceutical products (hereafter referred to "reference products"), to 'similar biological pharmaceutical products' (hereafter referred to as 'biosimilar') and to products which contain the same or closely related active substance but not authorized as biosimilar (hereafter referred to as 'related products').

The legal requirements for pharmacovigilance and the Egyptian good pharmacovigilance practices (GVP) apply to biologicals just as they do for other medicines. The guidance of this Chapter does not replace any of these. However, as outlined below, biologicals are associated with several specific challenges in pharmacovigilance.

Although separate guidance exists on donor traceability of pharmaceutical substances derived from blood and plasma, the general principles of pharmacovigilance and patient traceability in this Chapter also apply to such products. Other guidelines with pharmacovigilance requirements for specific biosimilars shall also be considered.

13.1.1. Pharmacovigilance aspects specific to biologicals

Unlike chemically synthesized medicines which can usually be easily characterized and reproduced across different manufacturers, biological active substances are complex molecules produced usually using complex manufacturing processes with many upstream or downstream steps that shape the overall safety, quality and efficacy profile.

The manufacturing process (including choice of cell line, raw or starting materials, fermentation and purification process, final formulation) is as much a determinant of the product's quality as the active substance, and minor changes in any manufacturing step can affect the product quality, and subsequently its safety and efficacy. Advances in biotechnology and analytical sciences will continue to allow greater characterization and control of biologicals, but it is this fundamental complexity that creates the specific challenges for biologicals in pharmacovigilance.

13.1.2. Immunogenicity

For biologicals and non-biologicals however, due to their much more complex nature, biologicals pose a greater potential risk of immunogenicity compared to non-biologicals and require specific consideration.

In most cases, immunogenicity to a biological will be without clinical significance, such as a transient appearance of antibodies, and will not impact on the risk-benefit balance of the product. However, on some occasions, immunogenicity could result in serious and life-threatening reactions.

Sources of immunogenicity for biologicals are multi-factorial and involve one or more product-related factors (e.g., choice of cell line, post-translational changes and alterations to the 3D structure during downstream processing, impurities, choice of product containers), treatment-related factors (e.g., route of administration, dosing frequency) and patient or disease-related factors (e.g., genetic background, concomitant medications, nature of the underlying disease and immune status).

Following on from characterization of immunogenicity at the time of initial marketing authorization, the next challenge relevant to any biological relates to changes to manufacturing or quality, and the fact that immunogenicity can potentially be introduced or altered at any time post-authorization potentially resulting in an altered safety or efficacy profile of a product.

Immunogenicity shall be reflected in the risk management plan (RMP).

If immunogenicity is included in the safety specification, relevant strategies for the evaluation of immunogenicity and associated clinical consequences in the post-authorization setting shall be proposed as an additional pharmacovigilance activity. Depending on the nature of any potential immunogenicity and the data that generated the concern, or the nature of the missing information, the additional pharmacovigilance activities shall have clearly defined objectives. The plan may include bio-analytical methods (e.g., in vitro assays, serology studies), non-clinical studies, interventional clinical studies or observational epidemiological approaches. Any analytical and clinical endpoints relevant to the potential risk, including those related to safety and efficacy (e.g., in order to evaluate potential effects of neutralizing antibodies), shall be clearly defined to support their characterization in passive surveillance (e.g., via targeted follow up), additional pharmacovigilance activities or epidemiological studies.

For these reasons, determination of the optimal strategy for evaluation of immunogenicity in the RMP shall be a multidisciplinary approach, with input from experts in the quality, non-clinical, clinical, pharmacovigilance and epidemiological fields. If a new clinical risk is identified that may have an immunogenic etiology, it shall be fully explored in any subsequent risk evaluation. Whether the risk is specific to a specific product or batch, the potential root cause shall be assessed in order to evaluate the ability for risk minimization or elimination (e.g., improved assays, manufacturing steps).

13.1.3. Manufacturing variability

Marketing authorization holders of pharmaceutical products make frequent changes to the manufacturing process of their products post-authorization. This happens for many reasons including for example changes in source materials, facilities or regulatory requirements.

Manufacturing changes may be more complex for biologicals.

These potential changes are relevant not only within a product (e.g., change in quality specifications over time), but also across products with the same international non-proprietary name (INN). In the long-term post-authorization period, the reference product, biosimilars and related products may potentially exhibit different safety profiles as these products evolve through their life-cycle.

13.1.4. Product traceability

As a consequence of manufacturing variability over time in the post-authorization phase within and across products with similar active substances, a key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in clinical use. This is especially important for biologicals compared to chemically-synthesized medicines due to a greater inherent variability in product characteristics.

Whether reference product, biosimilar or related product, it is essential that different products with the same INN can be readily distinguishable in order that newly emerging and product-specific safety concerns and immunogenicity are rapidly detected and evaluated throughout a product life-cycle, and that supply can be traced to locations and patients if necessary. As any given product usually retains the same product name following a significant change to manufacturing process, batch traceability is an important aspect to be considered in any associated updates to risk management plans.

As product name and batch information is included in the product packaging, this information is available to be recorded and reported at all levels in the supply chain from manufacturer release to prescription, dispensing and patient administration. Biologicals constitute a very diverse array of products for a wide range of therapeutic areas and the clinical settings for prescription, dispensing, supply and administration are equally diverse. Traceability needs therefore to be fully integrated in different healthcare settings and infrastructure that may vary across products and between countries, such as the infrastructure for electronic data recording and record linkage. Most products will be supplied in a hospital setting and, if record linkage does not exist, other methods need to be used to collect exposure information, such as routine bar code scanning at all points in the supply chain.

13.2. Structures and processes

13.2.1. Risk management system

As a general principle, any post-authorization update to the RMP for a reference product shall be similarly applied to the relevant biosimilar and related products, and vice-versa, unless justified, all parts of a RMP – Integrated RMP- are required for a biosimilar, with the exception of RMP part II, module SI “Epidemiology of the target population”.

13.2.1.1. Content of the risk management plan (RMP)

RMP part I “Product overview”

The origin of an active substance of a biological shall be included as important information about its Composition

RMP part II “Safety specification”

- **module SVI “Additional EU requirements for the safety specification”**

For all biologicals, the potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process shall be presented in relation to the potential for transmission of infectious agents.

- **module SVII "Identified and potential risks" and module SVIII "Summary of the safety concerns"**

The safety specification shall include important identified risks, important potential risks and missing information.
For biosimilar and related products, the summary of safety concerns shall, as a minimum, be the same as the reference product unless otherwise justified.
Immunogenicity shall specifically be addressed in this context and reflected in the RMP.

RMP part III "Pharmacovigilance plan"
The need and plans for continuous life-cycle signal detection and pharmacovigilance specific to the product including batch-specific issues, particularly following a significant change to the manufacturing process, shall be discussed. In this context, the pharmacovigilance plan shall include a discussion around clinical settings of product use and how this may impact on routine product name and batch recording and reporting (e.g., whether used in primary or tertiary care) and what additional activities or risk minimization measures may be required to support product traceability (e.g., provision of 'sticky' labels, bar coding).

- **Routine pharmacovigilance activities**

In this section, the marketing authorization applicant or holder shall discuss:

- The clinical settings of product use and how this may impact on product name and batch recording and reporting.
- Measures that will be introduced to routinely follow-up on case reports to obtain information on product name and batch number(s).
- Signal detection activities performed to identify batch-specific safety issues.
- Any adverse events of special interests (AESIs), with definitions, identified as important potential risks for which specific safety surveillance will be put in place.

- **Additional pharmacovigilance activities**

In this section, the marketing authorization applicant or holder shall discuss:

- Any additional measures introduced to support traceability of the product (e.g., provision of "sticky" labels, bar coding);
- Activities performed to measure background rates for AESIs, preferably by indication, in the age group targeted by the product;
- Activities performed to continuously monitor suspected adverse reaction reporting frequencies or rates for AESIs based on available data on exposure and comparing such rates to relevant defined background rates (using methods such as 'observed vs expected' analyses)
- Use of existing patient registries or other data sources (or establishment of a new registry if existing data sources are inadequate)
- For a biosimilar, any specific safety monitoring imposed on the reference product shall be adequately addressed in the pharmacovigilance plan of the biosimilar.

Post-authorization safety studies
The most optimal study design shall be used considering the objective of the post-authorization safety study (PASS). If an existing registry is to be used or a new registry is to be established, a

comparator or non-exposed group shall preferably be included. Joint disease registries shall be encouraged.

Biosimilar and related products
Any specific safety monitoring imposed on the reference product shall be adequately addressed in the pharmacovigilance plan, unless otherwise justified (e.g., if the safety concern was specific to the reference product and not included in the safety specification of the biosimilar or related product).

RMP part V "Risk minimization measures"
Risk minimization activities in place for the reference product shall, in principle, be included in the RMP of the biosimilar and related products, and vice-versa. Any deviation from this (e.g., when the risk minimization is linked specifically to the reference product) shall be justified.

Evaluating the effectiveness of additional risk minimization measures is necessary to establish whether an intervention has been effective or not, and if not why and which corrective actions are necessary. The evaluation shall be performed for the additional risk minimization tools individually and for the risk minimization program as a whole.

Effectiveness evaluation shall be conducted at the most appropriate time, accounting for time required for launch of the risk minimization measures, the estimated use of the product by the healthcare system and other relevant circumstances.

To evaluate the effectiveness of additional risk minimization measures two categories of indicators shall be considered, process indicators and outcome indicators.

- **Regarding post marketing pharmacovigilance activities:**
  Marketing authorization holders of all biological products are obligated to:
  - Individual Case Safety Reports (ICSRs) management
  - Periodic Benefit Risk Evaluation Report (PBRER) submission
  - Full signal management processes
  - Emergency Safety Issues (ESIs) notification
  - Comprehensive literature screening in national (for countries where the product is marketed in) and well-known international journals.
  - Any other pharmacovigilance activities required by EDA

14. Annex I: Definition

Audit:
A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled.

Auditee:
[Entity] being audited.

Audit finding(s):
Results of the evaluation of the collected audit evidence against audit criteria. Audit evidence is necessary to support the auditor‘s results of the evaluation, i.e. the auditor‘s opinion and report. It is cumulative in nature and is primarily obtained from audit procedures performed during the course of the audit.

Audit plan:
Description of activities and arrangement for an individual audit.

Audit programme:
Set of one or more audits planned for a specific timeframe and directed towards a specific purpose.

Audit recommendation:
Describes the course of action management might consider to rectify conditions that have gone awry, and to mitigate weaknesses in systems of management control.

Audit recommendations shall be positive and as specific as possible. They shall also identify who is to act on them.

Auditors ‘independence:
The freedom from conditions that threaten objectivity or the appearance of objectivity. Such threats to objectivity shall be managed at the individual auditor, engagement, functional and organizational levels.

Auditors ‘objectivity:
An unbiased mental attitude that allows internal auditors to perform engagements in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires internal auditors not to subordinate their judgment on audit matters to that of others.

Biological Products:
Products containing one or more active ingredients produced or derived from a biological source, including but not limited to, human vaccines, serums, blood and plasma products and derivatives, and also products manufactured using biotechnology and the like, as well as, any products or substances that may be created based on science updates and/or international standards and references.

Compliance:
Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements.

Control(s):
Any action taken by management and other parties to manage risk and increase the likelihood that established objectives and goals will be achieved. Management plans, organizes, and directs the performance of sufficient actions to provide reasonable assurance that objectives and goals will be achieved.

Day Zero: Confirmed/Verified signal:
A validated signal which, following further assessment, has been determined to be "true" i.e. a causal association can be established. For tracking purposes, signal status may be marked as: 'Assessed - for action'.

It is the first day when a notified competent authority or marketing authorization holder gets knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday.

Emerging safety issue:
A safety issue considered by a MAH to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the pharmaceutical product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Evaluation (of audit activities):
Professional auditing bodies promote compliance with standards, including in quality assurance of their own activities, and codes of conduct, which can be used to address adequate fulfilment of the organization's basic expectations of Internal Audit activity and its conformity to internationally accepted auditing standards.

Finding(s):
See Audit findings.

Healthcare professional:
For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners.

Head of the organization:
See Upper management.

ICH E2B (R2):
E2B R2 is an international standard for transmitting medicine adverse event reports specified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E2B (R3):
ICH E2B (R3) data elements have a hierarchical tree structure. It consists of two major sections A and B, where A contains administrative and identification information, and B contains information on the case. The subsidiary sections are categorized by the nature of the data, and are:

- Section A
  C.1 - Identification of the Case Safety Report

  C.2- Primary Source(s) of Information

  C.3 - Information on Sender of Case Safety Report

  C.4 - Literature Reference(s)

  C.5 - Study Identification

- Section B
  D- Patient Characteristics

  E- Reaction(s)/ Event(s)

  F- Results of Tests and Procedures Relevant to the Investigation of the Patient

  G- Drug(s) Information

  H- Narrative Case Summary and Further Information

In addition to the letters ‘i’ and ‘k’ indicating iterations of the event (E.i) or the drug (G.k), the letter ‘r’ is used to indicate that the data element or the section is repeatable

Identified risk:
An untoward occurrence for which there is adequate evidence of an association with the pharmaceutical product of interest. Examples include: an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;

an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;

an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure."

Indeterminate signal:
It is primarily a validated signal which is determined with further assessment to be inconclusive (i.e., a causal association cannot be established at that point of time) due to lack of information or insufficient specificity of data. In the context of risk management, it is considered as “an untoward occurrence in which there is some basis for suspicion of an association with the pharmaceutical product of interest but where this association has not been

confirmed". For tracking purposes, signal is refuted and its status may be marked as ('Assessed - no action' or 'Monitor').

Inspection grading:

- Critical deficiency

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines. Deficiencies classified as critical may include a pattern of deviations classified as major. A critical deficiency also occurs when an engagement in fraud, misrepresentation or falsification of data is detected.

- Major deficiency

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines. Deficiencies classified as major may include a pattern of deviations classified as minor.

- Minor deficiency

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients. A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Internal Control:

Internal control is an integral process that is effected by an entity's management and personnel and is designed to address risk and provide reasonable assurance that in pursuit of the entity's mission, the following general objectives are being achieved: executing orderly, ethical, economical, efficient and effective operations, fulfilling accountability obligations, complying with applicable laws and regulations and safeguarding resources against loss, misuse and damage (for further information refer to COSO standards).

Medical products:

Any product or article containing substance or a group of substances used for the purpose of treatment or prevention or diagnosis in humans or animals or which can be described as having another medical effect or which aims to restore, correct or modify physiological functions through having a pharmacological, immunological, or metabolic effect on general health, all of which in accordance to the applicable references and standards, as well as, any products or substances that may be created through advances in science and/or international references and standards.

Missing information:

Gaps in knowledge about the safety of a pharmaceutical product for certain anticipated utilization (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized

so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning shall focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP."

Natural person
Is a real human being, as distinguished from a corporation which is often treated at law as a fictitious person.

Non-validated signal:
A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted. For tracking purposes, signal status may be marked as: 'non-validated – known' (i.e., labelled/listed, flagged in other regulatory documents (e.g., PBRER, RMP) or previously alerted by other regulatory authorities, etc.) or 'non-validated – other' (i.e., due to confounders more likely cause the risk, contradicting time to onset, poor disease prognosis, etc.).

Null Flavors:
The null Flavors are a collection of codes specifying why a valid value is not present in an ICSR. They are available with the ICH-E2B(R3) format and not with ICH-E2B(R2). They refer to instances, where for example a proper value is applicable, but not known (e.g. age of the patient is unknown: code UNK), or where the information is available to a sender of an ICSR but it is masked because it cannot be provided due to security, privacy or other reasons (e.g. date of birth of the patient cannot be shared due to local data protection laws: code MSK).

Pharmaceutical products:
Shall mean for purposes of this guideline medical and biological products**.**

Pharmacovigilance sub-system file.
The national Pharmacovigilance sub-system file (national PSSF) for multinational companies that describes the Pharmacovigilance sub-system at the national level.

Pharmacovigilance system master file (PSMF):
A detailed description of the pharmacovigilance system used by the marketing authorization holder
with respect to one or more authorized pharmaceutical products.

Pharmacovigilance system:
A system used by the marketing authorization holder and by EDA to fulfil the pharmacovigilance tasks and responsibilities listed in national regulations and designed to monitor the safety of authorized pharmaceutical products and detect any change to their risk-benefit
balance.

In general, a pharmacovigilance system is a system used by an organization to fulfil its legal tasks
and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized pharmaceutical products and detect any change to their risk-benefit balance.

Pharmacovigilance:
The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.

Potential risk:
An untoward occurrence for which there is some basis for suspicion of an association with the pharmaceutical product of interest but where this association has not been confirmed. Examples include:

1. Toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;

2. Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship;

3. A signal arising from a spontaneous adverse reaction reporting system;
4. An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the pharmaceutical product."

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.
This applies for the purpose of fulfilling quality requirements.

Quality improvements:
Correcting and improving the structures and processes where necessary.
This applies for the purpose of fulfilling quality requirements.

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

Quality planning:
Establishing structures and planning integrated and consistent processes.
This applies for the purpose of fulfilling quality requirements.

Quality requirements:
Those characteristics of a system that are likely to produce the desired outcome, or quality objectives.

Quality system of a pharmacovigilance system:
The organizational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.
The quality system is part of the pharmacovigilance system.

Refuted/Indeterminate signal:
A validated signal which, following further assessment, has been determined to be "false" or "inconclusive" or "indeterminate" i.e. a causal association cannot be established at that point in time. For tracking purposes, signal status may be marked as: 'Assessed - no action', or 'Monitor'.

Risk management plan:
A detailed description of the risk management system.

Risk management system:
A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to pharmaceutical products including the assessment of the effectiveness of those activities and interventions"

Risk minimization activity (used synonymously with risk minimization measure):
An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity shall it occur.

Routine pharmacovigilance activities:
Routine pharmacovigilance is the primary/minimum set of activities required for all pharmaceutical products and shall be implemented for all safety concerns, it includes for example but not restricted to preparation of PBRER, Adverse events reporting, continuous monitoring & evaluation of the efficacy and safety profile, literature search and Signal detection, which is part of routine pharmacovigilance, is an important element in identifying new risks for all products. "

Safety concern:
An important identified risk, important potential risk and missing information. Safety observation. It is prior to signal detection. A safety observation may originate from one or multiple sources, including, scientific literature. This safety observation justifies earliest judgment to evaluate existence/non-existence of a hypothesis suggesting a new potentially causal association, or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial.
Signal assessment. The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the

active substance or pharmaceutical product or whether known risks have changed. This review may include nonclinical and clinical data and shall be as comprehensive as possible regarding the sources of information.

Signal management:
A set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a pharmaceutical product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

Signal prioritization:
The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the pharmaceutical product and thus require careful attention and management.

Signal status:
It defines the final/primary status of a detected signal throughout the signal management process. Signal status can be marked as: 'non-validated – known', 'non-validated – other', 'Validated - for assessment', 'Assessed - for action', 'Assessed - no action', or 'Monitor'.

Signal validation:
The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Signal:
According to the WHO, signal is defined as the reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Signal is also interpreted as information arising from one or multiple sources, including observations and experiments which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. New aspects of a known association may include changes in the frequency, distribution (e.g., gender, age and country), duration, severity or outcome of the adverse reaction. A signal often relates to all pharmaceutical products containing the same active substance, including combination products. Some signals may only be relevant for a particular pharmaceutical product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of pharmaceutical products.

Solicited Report:
Solicited reports of suspected adverse reactions are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare professionals, compassionate use or name patient use, or information gathering on efficacy or patient compliance.

Target population (treatment):
The patients who might be treated with the pharmaceutical product in accordance with the indication(s) and contraindications in the authorized product information"

Unsolicited Report:
A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorization holder or other organization (e.g. regional pharmacovigilance center, poison control center) that describes one or more suspected adverse reactions in a patient who was given one or more pharmaceutical products.

Upper management:
Group of persons in charge of the highest executive management of an organization. Membership of this group is determined by the governance structure of the organization. While it is envisaged that the upper management usually is a group, the head of the organization is the one person at the top of the organization with ultimate responsibility for ensuring that the organization complies with relevant legislation.

Validated signal:
A signal for which the signal validation process has concluded that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. For tracking purposes, signal status may be marked as: 'Validated - for assessment' (earlier within the signal management process), 'Assessed - for action', 'Assessed - no action', or 'Monitor'.

XML:
XML, or Extensible Markup Language, is a markup language that defines rules for structuring documents in a format that can be read by both humans and machines. The structure of XML is based on a grouping of sections and elements that are annotated by start and end tags. Tags are user-friendly phrases used to indicate the data elements contained within the tags. For example, using the E2B R2 format a patient's date of birth of 19 March 1972 in XML would appear as: <patient birthdate>19720319</patient birthdate>.

For more definitions, refer to EMA GVP Annex I. Definitions.

15. Annex II: Abbreviations

ADR	Adverse drug reaction (preferred term: Adverse reaction)
AE	Adverse event
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
AR	Assessment report
ATC	Anatomical- therapeutic-chemical (in Anatomical Therapeutic Chemical Classification System)
ATMP	Advanced therapy pharmaceutical product
CCDS	Company core data sheet
CCSI	Company core safety information
CIOMS	Council for International Organizations of Medical Sciences
COSO	Committee of Sponsoring Organizations of the Treadway Commission
DB	Database
DDPS	Detailed description of the pharmacovigilance system
DHPC	Direct healthcare professional communication
DIBD	Development international birth date
DLP	Data lock point
DSUR	Development safety update report
DUS	Drug utilization study
eCTD	Electronic Common Technical Document
EDA	Egyptian Drug Authority

ENCePP	European Network of Centre for Pharmacoepidemiology and Pharmacovigilance
EPVC	Egyptian Pharmaceutical Vigilance Center
ESTRI	ICH electronic standards for the transfer of regulatory information
EU	European Union
EURD	EU reference date
GCP	Good clinical practice
GDP	Good distribution practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPP	ISPE Guidelines for good Pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HLT	High-level term (in MedDRA)
IBD	International birth date
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual case safety report
IIA	Chartered Institute of Internal Auditors
IME	Important medical event
INN	International non-proprietary name
ISO	International Organization for Standardization
ISPE	International Society for Pharmacoepidemiology
IT	Information technology

LSR	Local Safety Responsible
MA	Marketing authorization
MAH	Marketing authorization holder
MedDRA	ICH Medical Dictionary for Regulatory Activities
NIMP	Non-investigational pharmaceutical product
O/E	Observed-versus-expected analysis
P.	Product- or Population-Specific Considerations (in GVP)
PAES	Post-authorization efficacy study
PAS	Post-authorization study
PASS	Post-authorization safety study
PBRER	Periodic benefit-risk evaluation report
PhV DB	Pharmacovigilance database
PL	Package leaflet
PSMF	Pharmacovigilance system master file
PSSF	Pharmacovigilance sub-system file (on national level)
PBRER	Periodic safety update report
PT	Preferred term (in MedDRA)
PV GA	Pharmaceutical Vigilance General Administration
QPPV	Qualified person responsible for pharmacovigilance
RMP	Risk management plan
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query

SOC	System organ class (in MedDRA)
SUSAR	Suspected unexpected serious adverse reaction
UMC	Uppsala Monitoring Centre
URD	Union reference date (preferred term: EU reference date)
WHO	World Health Organization

16. Annex III: Templates

Annex III.1. Template of the Egyptian Display of the Risk Management Plan (RMP) - for MAH/Applicant having EU/global RMP

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorization Holder or Applicant:	
Name of the pharmacovigilance representative (if applicable)	
Number of pharmaceutical products to which this Egyptian display of RMP refers:	Choose one of the following: 1 2 3
Product(s) concerned (brand name(s)):	<list>

Version number of Egyptian Display | < Enter a version no >

Date of final sign off | <Enter a date>

For the EU/global RMP which is the reference of this Egyptian Display (referenced EU/global RMP):

Version number	< Enter a version no >

Table of content of Egyptian Display of the RMP

Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimization activities will need to **be tailored** to the system in place in a particular country or global region. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a pharmaceutical product may also vary between regions. Therefore, a product may **need different or supplementary activities in the RMP** for each region although there will be core elements which are common to all. For example, much of the safety specification will be the same regardless of where the pharmaceutical product is being used but the epidemiology of the disease may vary, and there may be **additional or fewer safety concerns** depending upon the target population and indication.

MAH/Applicants having EU RMP in place submit both of the following:

The most updated version of the EU/global RMP (referenced EU/global RMP including its annexes); altogether with The Egyptian Display of the RMP (including its annexes).

In these circumstances (submitting the Egyptian Display and the EU/global RMP), the following conditions apply:

- *When the referenced EU/global RMP is subject to update the Egyptian Display of RMP shall be updated in accordance.*
- *Minor differences may exist between this guidance and the EU/global RMP, in this case MAH/Applicant may be asked by Pharmaceutical Vigilance General Administration to submit additional information, use different tables, and/or provide clarification…. etc.*
- *The submitted EU/global RMP shall be the most updated version.*
- *The EU/global RMP shall be submitted with its annexes and reference materials*
- *Generally, it is required that all the risk management activities applied globally/in the EU/global to be applied in Egypt as well, especially the risk minimization measures including the measurement of their effectiveness. Accordingly, all activities, action plans and details especially the risk minimization ones (including the measurement of their effectiveness) stated in the submitted EU/global RMP are expected by default to apply in Egypt and the MAH is required to adhere to them, EXCEPT otherwise clearly stated and justified by the MAH/Applicant in the "Egyptian Display of the RMP" and agreed by Pharmaceutical Vigilance General Administration. Please pay attention in filling in the Egyptian Display of RMP and do not skip any activity which was in the reference EU/global RMP without highlighting whether it will be implemented or not on Egypt according to the tables below. Any unjustifiably skipped activity will be considered as "apply to national level" and the MAH is required to adhere to.*

The purpose of the "Egyptian Display of the RMP" is:

- To highlight to what extent the risk management activities proposed to be implemented nationally adhere to the globally implemented plan and;
- To provide justification for any difference (apart from what implemented globally) whenever exist including the needed national tailoring if any.

- In addition, it shall include an assessment whether there are any additional specific risks or not, describing there may be added activities to manage those additional risks.
- It provides good evidence that the LSR has clear understanding and commitment about the activities that will be implemented on Egypt and how they will be implemented.

Contacts

Local Safety Responsible (LSR) name ……

LSR signature ……..

Contact person for this RMP……..

E-mail address or telephone number of contact person…….

Section I: Product(s) Overview

For each product in the RMP

Indication(s)	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product
	Proposed (if applicable) **in Egypt**
	That of the reference pharmaceutical product
Posology and route of administration in Egypt	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product
	Proposed (if applicable) **in Egypt**
	That of the reference pharmaceutical product

Pharmaceutical form(s) and strengths	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product
	Proposed (if applicable) **in Egypt**
	That of the reference pharmaceutical product

Date of first authorization (if authorized) in Egypt <Enter a date>

Section II: Summary table of Safety concerns

Copy table from Part II: SVIII of the referenced EU/global RMP and add to the list any risk which may be specific to Egypt.

Summary of safety concerns	
Important identified risks	□ < > List □ Egypt-specific risk (if any): < > List
Important potential risks	□ < > List □ Egypt-specific risk (if any): < > List
Missing information	□ < > List □ Egypt-specific risk (if any): < > List

Section III: Summary of the Risk Management Plan by activity

III.1 Activities included in the referenced EU/global RMP

The following table shall summarize all the activities stated in the referenced EU/global RMP, separate table for each pharmaceutical product included in the Egyptian Display of RMP may be provided as appropriate. It shall be organized **in terms of the activities/actions** to be undertaken rather than by safety concern. The reason for this is that one proposed activity (e.g. a prospective safety cohort study) could address more than one of the safety concerns.

All the activities of the following types shall be covered in the table; in addition, indicate the corresponding type in the second column:

- Routine pharmacovigilance activities,
- Ongoing &planned additional pharmacovigilance activities,
- Ongoing &planned post authorization efficacy studies
- Routine risk minimization measures
- Additional risk minimization measures

Those activities as stated in the referenced EU/global RMP shall be displayed in comparison with those proposed by the MAH/Applicant to be implemented in Egypt; any difference shall be clearly justified. Ideally the following **activity comparison table** can be used to present the needed data.

Activities as stated in the referenced EU/global RMP	Type of the activity	Safety Concern	Action plan in the referenced EU/global RMP	Action plan in the Egyptian Display of the RMP	Highlight differences if any (even minor difference)	Justification

If the MAH/Applicant proposes **not to implement** in Egypt, any of the **activities** stated in the referenced RMP; this shall be clearly highlighted in the above table and comprehensive justification shall be supplied, in addition explanation of how the safety concern intended by this activity will then be managed in Egypt.

If the MAH/Applicant proposes some differences (even minor ones) in the action plan of **specific activity** to be followed in Egypt other than those described in the referenced RMP; the differences shall be clearly highlighted in the table and comprehensive justification shall be supplied as well.

III.2 Supplementary activities in Egypt

If the MAH/Applicant will implement in Egypt additional activities over those stated in the referenced RMP (e.g. due to specific safety concern/s or due to other justified reason); this shall be presented in details according to the below tables, as appropriate **any relevant documents shall be annexed**. It is also important to realize that for activities already exist in the referenced RMP but different action plan in Egypt is proposed by MAH/Applicant this action plan cannot be included in this section as if it is plan for additional activity, instead the difference shall be described in the above table.

a. **Supplementary pharmacovigilance activity(s)**

If the supplementary activity is a specific questionnaire is planned for collecting structured data on a safety concern of special interest on Egypt this is still considered to be routine but shall be mentioned and a mock up provided in this Egyptian Display of RMP annex 4. If the supplementary activity(s) is of additional pharmacovigilance type (i.e. additional pharmacovigilance activity);

fill in the following table, and protocols shall be provided in Annex 3 of this Egyptian Display of RMP

Study/activity Type, title	**Objectives**	**Safety concerns addressed (country/region specific)**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**

b. **Supplementary post-authorization efficacy study(s)**

If the supplementary activity(s) is a post-authorization study fill in the following table. The protocols shall be provided in Annex 3 of this Egyptian Display of RMP.

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**

c. **Supplementary risk minimization activity(s)**

If the supplementary activity(s) is of risk minimization type (i.e. risk minimization activity); fill in the following tables. Details shall be provided in Annexes 6 of this Egyptian display of RMP.

Safety concern	
Objective(s) of the risk minimization measures	
Routine risk minimization measures	(Proposed) text in SmPC <E.g. Dose reduction for ……. in section 4.2 of the SPC…… Warning in section 4.4 to…… Listed in section 4.8>

	Comment (e.g. on any differences between SmPCs)
	Other routine risk minimization measures <E.g. Prescription only medicine Use restricted to physicians experienced in the treatment of…….>
Additional risk minimization measure(s)1	Objective and justification of why needed.
	Proposed actions/components and rationale
Additional risk minimization measure(s) 2 (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale

Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	*If a study is planned, this shall also be included in Part III.2 Additional PhV activities to assess effectiveness of risk minimization measures*
Criteria for judging the success of the proposed risk minimization measures	
Planned dates for assessment	
Results of effectiveness measurement	Provide latest assessment at each update of the RMP. For risk minimization measures where formal studies are planned, any results shall be mentioned in Part III.2 with the implications discussed here and any remedial actions in V.2
Impact of risk minimization	
Comment	

Section IV: Egyptian Display of RMP Annexes

Part VII: RMP Annexes

List of annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory reviewwith this updated version of the RMP

Part B: Requested amendments of previously approved protocols of studies in the PharmacovigilancePlan, submitted for regulatory review with this updated version of the RMP

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by EDA

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Annex 7 - Other supporting data (including referenced material

Annex 8 - Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change

Annex III.2. Template of the Risk Management Plan (RMP) in Egypt in integrated format

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorization Holder or Applicant:	
Name of the pharmacovigilance representative (if applicable)	
Number of pharmaceutical products to which this RMP refers:	Choose one of the following: 1 2 3
Product(s) concerned (brand name(s)):	<list>

Data lock point for this RMP <Enter a date> Version number <Enter a version no>

Date of final sign off <Enter a date>

RMP table of content

Part I: Product(s) Overview

Part II: module SI - Epidemiology of the indication(s) and target population

Part II: module SII - Non-clinical part of the safety specification

Part II: module SIII - Clinical trial exposure

Part II: module SIV - Populations not studied in clinical trials

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SV.1 Post-authorization exposure

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Part II: module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.3 Details of important identified risks, important potential risks, and missing information

Part II: module SVIII - Summary of the safety concerns

Part III: Pharmacovigilance Plan (including post-authorization safety studies)

III.1 Routine pharmacovigilance activities

III.2 Additional pharmacovigilance activities

III.3 Summary Table of additional Pharmacovigilance activities

Part IV: Plans for post-authorization efficacy studies

Part V: Risk minimization measures

V.1. Routine Risk Minimization Measures

V.2. Additional Risk Minimization Measures

V.3. Summary of risk minimization measures

Part VI: Summary of the risk management plan by product

II.1 List of important risks and missing information

II.2 Summary of important risks

II.3 Post-authorization development plan

II.3.1 Studies which are conditions of the marketing authorization

II.3.2 Other studies in post-authorization development plan

Part VII: RMP Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Part I: Product(s) Overview

Administrative information on the RMP

Part	**module/annex**	**Date last updated for submission (sign off date)**	**Version number of RMP when last submitted**

Part II Safety Specification	SI Epidemiology of the indication and target population(s)	<Enter a date>	
	SII Non-clinical part of the safety specification	<Enter a date>	
	SIII Clinical trial exposure	<Enter a date>	
	SIV Populations not studied in clinical trials	<Enter a date>	
	SV Post-authorization experience	<Enter a date>	
	SVI Additional requirements for the safety specification	<Enter a date>	
	SVII Identified and potential risks	<Enter a date>	
	SVIII Summary of the safety concerns	<Enter a date>	
Part III Pharmacovigilance Plan		<Enter a date>	
Part IV Plan for post-authorization efficacy studies		<Enter a date>	
Part V Risk Minimisation Measures		<Enter a date>	
Part VI Summary of RMP		<Enter a date>	
Part VII Annexes	Annex 1 – EudraVigilance Interface.	<Enter a date>	
	Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	<Enter a date>	
	Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	<Enter a date>	
	Annex 4 - Specific adverse drug reaction follow-up forms programme	<Enter a date>	

	Annex 5 - Protocols for proposed and on-going studies in RMP part IV	<Enter a date>	
	Annex 6 - Details of proposed additional risk minimization activities (if applicable)	<Enter a date>	
	Annex 7 - Other supporting data (including referenced material)	<Enter a date>	
	Annex 8 – Summary of changes to the risk management plan over time	<Enter a date>	

A new RMP version number shall be assigned each time any Parts/modules are updated

QPPV name:……

QPPV signature: ……

Contact person for this RMP:……..

E-mail address or telephone number of contact person:…….

Overview of versions:

Version number of last agreed RMP:

Version number	<Enter a version no>
Agreed within	<Indicate procedure>

Current RMP versions under evaluation:

RMP Version number	**Submitted on**	**Submitted within**
<Insert number>	<Enter a date>	<indicate procedure >
… etc.		

For each product in the RMP

Invented name(s) in Egypt	

Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	
Indication(s)	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product
	Proposed (if applicable) **in Egypt**
	That of the reference pharmaceutical product
Posology and route of administration	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product
	Proposed (if applicable) **in Egypt**
	That of the reference pharmaceutical product
Pharmaceutical form(s) and strengths	Current (if applicable) **in Egypt**
	Current of the reference pharmaceutical product

	Proposed (if applicable) **Egypt**
	That of the reference pharmaceutical product

Country and date of first authorization worldwide	<Enter a country> <Enter a date>
Country and date of first launch worldwide	<Enter a country> <Enter a date>
Date of first authorization (if authorized) in Egypt	

Is the product subject to additional monitoring? Yes ☐ No ☐

Part II: module SI - Epidemiology of the indication(s) and target population

<Indication >

- Incidence:
- Prevalence:
- Demographics of the population in the <authorized> <proposed> indication – <age, gender, racial and/or ethnic origin> and risk factors for the disease:
- The main existing treatment options:
- Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:
- Important co-morbidities:

Part II: module SII - Non-clinical part of the safety specification

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Toxicity including: - **Single and repeat-dose toxicity,** - **Reproductive (shall be discussed if medicine might be used in women of child-bearing potential)** - **Developmental toxicity** - **Nephrotoxicity** - **Hepatotoxicity** - **Genotoxicity** - **Carcinogenicity**	
General safety pharmacology:	
- Cardiovascular (including potential for QT interval prolongation) - Nervous system	
Mechanisms for drug interactions	
Other toxicity-related information or data	

Conclusions on non-clinical data

List of safety concerns from non-clinical data that have:

- Been confirmed by clinical data
- Have not been adequately refuted by clinical data
- Which are of unknown significance
- Or where further research needed

Safety concerns
Important identified risks (confirmed by clinical data)
Important potential risks (not refuted by clinical data or which are of unknown significance)
Missing information

These safety concerns shall be carried forward to Part II module SVIII.

Part II: module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Provide details of how the authorized indications and target populations have developed during the lifecycle for the product(s) within this RMP. This shall include:

- Original indication /product name(s)
- New populations e.g. extensions of indications/ new products
- Any other significant developments – e.g. route of administration

SIII.2 Clinical Trial exposure

The following tables shall be provided for each indication with a summary table showing total exposure.

Provide each table, where available, based on exposed (to pharmaceutical product of interest) persons in:

- Randomized, blinded trial population only
- All clinical trial populations (including open extension)

Table 1: Duration of exposure (by indication)		
Indication 1(person time shall only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		

12 m etc.		
Total person time		

Table 1: Duration of exposure (by indication)		
Indication 2 (person time shall only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

Table 2: Duration of exposure (totals)		
Total exposed population (person time shall only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

Table 3: By dose (by indication)		
Indication 1		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2 etc.		
Total		
Indication 2		

Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2 etc.		
Total		

Table 4: By dose (totals)		
Total Population		
Dose of exposure	Persons	Person time
Dose level 1		
Dose level 2 etc.		
Total		

Table 5: By age group and gender (by indication)				
Indication 1				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				
Indication 2				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 6: By age group and gender (by product)				
Total population by pharmaceutical product 1				
Age group	Persons		Person time	
	M	F	M	F

Age group 1				
Age group 2 etc.				
Total				
Total population by pharmaceutical product 2				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 7: By age group and gender (totals)				
Total population				
Age group	Persons		Person time	
	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 8: By ethnic or racial origin (by indication)		
Indication 1		
Ethnic/racial origin	Persons	Person time
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		
Indication 2		
Ethnic/racial origin	Persons	Person time
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 9: By ethnic or racial origin (totals)		
Total population		
Ethnic/racial origin	Persons	Person time

Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 10: Special populations (by indication)		
Indication 1		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism		
Immuno-compromised		
Indication 2		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism		
Immuno-compromised		

Table 11: Special populations (totals)		
Total population		
	Persons	Person time
Pregnant women		
Lactating women		
Renal impairment (specify or categorise)		
Hepatic impairment (specify or categorise)		
Cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism		
Immuno-compromised		

Part II: module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale:

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

<The clinical development programme is unlikely to detect certain types of adverse reactions such as <rare adverse reactions>, < adverse reactions with a long latency>, or those caused by <prolonged> or <cumulative exposure>.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	<not included in the clinical development program>
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different frominclusion criteria in clinical trials	<not included in the clinical development program>
Population with relevant different ethnic origin	<not included in the clinical development program>

Subpopulations carrying relevant geneticpolymorphisms	<not included in the clinical development program>
Other	<not included in the clinical development program>

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

SV.1.2 Exposure

Table SV.1.2: Exposure table by indication, <gender>, <age group>, <region>

Indication	Sex	Age (years)	Dose	Formulation	Region

Part II: Module SVI - Additional requirements for the safety specification

Potential for misuse for illegal purposes

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Identified/potential Risk ( )	
Frequency with 95% CI	
Seriousness/out comes	
Severity and nature of risk	
Background incidence/prevalence	
Risk groups or risk factors	
Potential mechanisms	
Preventability	
Impact on individual patient	
Potential public health impact of safety concern	
Evidence source	
MedDRA terms	

SVII.3.2. Presentation of the missing information

Part II: module SVIII - Summary of the safety concerns

A summary shall be provided of the safety concerns identified in previous modules (SII, SIV, SVI, and SVII) of Part II. A safety concern may be an:

- Important identified risk;
- Important potential risk; or
- Missing information.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- Safety concerns relating to the active substance;
- Safety concerns related to a specific formulation or route of administration;
- Safety concerns relating to the target population;
- Risks associated with switch to non-prescription status.

Division of safety concerns by headings shall only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

Table 3. Summary of safety concerns

Summary of safety concerns	
Important identified risks	<> List
Important potential risks	<> List
Missing information	<> List

Part III: Pharmacovigilance Plan (including post- authorization safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for <safety concerns>:

Other forms of routine pharmacovigilance activities for <safety concerns>:

III.2 Additional pharmacovigilance activities

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				

Category 3 - Required additional pharmacovigilance activities			

Part IV: Plans for post-authorization efficacy studies

Table Part IV.1: Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimisation activities

<Safety concern 1>	<Routine risk communication:> <Routine risk minimisation activities recommending specific clinical measures to address the risk:> <Other routine risk minimisation measures beyond the Product Information:>
<Safety concern 2>	

V.2 Additional Risk Minimization Measures

V.3 Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
<Safety concern 1>	<Routine risk minimization measures:>	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> <Additional pharmacovigilance activities:>
Safety concern	Risk minimization measures	Pharmacovigilance activities

Part VI: Summary of the risk management plan by product

This is a summary of the risk management plan (RMP) for <invented name>. The RMP details important risks of <invented name>, <how these risks can be minimised>, and how more information will be obtained about <invented name>'s risks and uncertainties (missing information).

<Invented name>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <invented name> shall be used.

VI.1 The medicine and what it is used for

<Invented name> is authorised for <indication outline – from Table Part I.1 – Indication(s)> (see SmPC for the full indication). It contains <INN> as the active substance and it is given by <route of administration – from Table Part I.1 "pharmaceutical form(s) and strengths">.

VI.2. Risks associated with the medicine and activities to minimize or further characterize the risks

VI.2.1. List of important risks and missing information

Important risks of <invented name> are risks that need special risk management activities to further investigate or minimize the risk, so that the pharmaceutical product can be safely <administered> <taken>. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <invented name>. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the pharmaceutical product that is currently missing and needs to be collected (e.g. on the long- term use of the medicine);

List of important risks and missing information (from Part II: Module SVIII)	
Important identified risks	<>
Important potential risks	<>
Missing information	<>

VI.2.2. Summary of important risks

<Important <identified> <potential> risk > or <Missing information>

Evidence for linking the risk to the medicine	
Risk factors and risk groups	

Risk minimization measures	<Routine risk minimization measures> <Additional risk minimization measures> <No risk minimization measures>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <Short study name> See section II.C of this summary for an overview of the post-authorization development plan.

<Important <identified> <potential> risk 2> or <Missing information>	
Risk minimization measures	<Routine risk minimization measures>

	<Additional risk minimization measures>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <Short study name> See section II.C of this summary for an overview of the post-authorization development plan.

VI.2.3. Post-authorization development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

VI.2.3.2. Other studies in post-authorization development plan

Part VII: RMP Annexes

List of annexes

Annex 1 – EudraVigilance Interface (If Applicable)

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by EDA

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Annex 7 - Other supporting data (including referenced material

Annex 8 - Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change

Annex III.3. Template of the Risk Management Plan (RMP) for Generics abridged format

Active substance(s) (INN or common name):	
Pharmaco-therapeutic group (ATC Code):	
Name of Marketing Authorization Holder or Applicant:	
Name of the pharmacovigilance representative (if applicable)	
Number of pharmaceutical products to which this RMP refers:	Choose one of the following: 1 2 3
Product(s) concerned (brand name(s)):	<list>

Data lock point for this RMP <Enter a date>

Version number <Enter a version no>

Date of final sign off <Enter a date>

Abridged RMP table of content

This guidance covers the Parts and modules of the abridged RMP which may be required for applications concerning generics. modules and sections in the RMP which are ALWAYS NOT required from generics are omitted in this guidance of abridged RMP. Please note that the naming and numbering of the parts, module s & sections are standardized thus shall NOT be changed due to the omission of unrequired sections.

Other sections of the abridged RMP apply to generics in ONLY certain situations as described below those have been provided her for completeness. Parts III and IV many not be required and applicants are encouraged to discuss the need with EDA prior to submission of the RMP.

Part I: Product(s) Overview

Administrative information on the RMP

Part	module /annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted/
Part II Safety Specification	SV Post authorization experience Only required for updates to the RMP	<Enter a date>	
	SVIII Summary of the safety concerns	<Enter a date>	
Part III Pharmacovigilance Plan	Only needed if reference product has additional PhV activities	<Enter a date>	
Part IV Plan for post-authorization efficacy studies	Only needed if reference product has imposed post-authorization efficacy studies	<Enter a date>	
Part V Risk Minimisation Measures		<Enter a date>	
Part VI Summary of RMP		<Enter a date>	
Part VII Annexes	Annex 1 – EudraVigilance Interface.	<Enter a date>	
	Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance	<Enter a date>	

	Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	<Enter a date>	
	Annex 4 - Specific adverse drug reaction follow-up forms programme	<Enter a date>	
	Annex 5 - Protocols for proposed and on-going studies in RMP part IV	<Enter a date>	
	Annex 6 - Details of proposed additional risk minimisation activities (if applicable)	<Enter a date>	
	Annex 7 - Other supporting data (including referenced material)	<Enter a date>	
	Annex 8 – Summary of changes to the risk management plan over time	<Enter a date>	

A new RMP version number shall be assigned each time any Parts/modules are updated

QPPV name:……

QPPV signature: ……

Contact person for this RMP:……..

E-mail address or telephone number of contact person:…….

Overview of versions:

Version number of last agreed RMP:

Version number	<Enter a version no>
Agreed within	<Indicate procedure>

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
<Insert number>	<Enter a date>	<indicate procedure >
… etc.		

For each product in the RMP

Invented name(s) in Egypt	
Brief description of the product including: chemical class summary of mode of action important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	
Indication(s)	Current (if applicable) in Egypt
	Current of the reference pharmaceutical product
	Proposed (if applicable) in Egypt
	That of the reference pharmaceutical product
Posology and route of administration	Current (if applicable) in Egypt
	Current of the reference pharmaceutical product
	Proposed (if applicable) in Egypt
	That of the reference pharmaceutical product
Pharmaceutical form(s) and strengths	Current (if applicable) in Egypt
	Current of the reference pharmaceutical product

	Proposed (if applicable) in Egypt
	That of the reference pharmaceutical product

Country and date of first authorization worldwide	<Enter a country>	<Enter a date>
Country and date of first launch worldwide	<Enter a country>	<Enter a date>
Date of first authorization (if authorized) in Egypt		

Is the product subject to additional monitoring? Yes ☐ No ☐

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

SV.1.2 Exposure

Table SV.1.2: Exposure table by indication, <gender>, <age group>, <region>

Indication	Sex	Age (years)	Dose	Formulation	Region

Part II: module SVIII - Summary of the safety concerns

A summary shall be provided of the safety concerns identified in previous modules (SII, SIV, SVI, and SVII) of Part II. A safety concern may be an:

- Important identified risk;
- Important potential risk; or
- Missing information.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- Safety concerns relating to the active substance;
- Safety concerns related to a specific formulation or route of administration;

- Safety concerns relating to the target population;
- Risks associated with switch to non-prescription status.

Division of safety concerns by headings shall only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

Table 3. Summary of safety concerns

Summary of safety concerns	
Important identified risks	<> List
Important potential risks	<> List
Missing information	<> List

Part III: Pharmacovigilance Plan (including post- authorization safety studies)

III.1 Routine pharmacovigilance activities

III.1.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for <safety concerns>:

Other forms of routine pharmacovigilance activities for <safety concerns>:

III.2 Additional pharmacovigilance activities

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				

Part IV: Plans for post-authorization efficacy studies

Table Part IV.1: Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimisation activities
<Safety concern 1>	<Routine risk communication:> <Routine risk minimisation activities recommending specific clinical measures to address the risk:> <Other routine risk minimisation measures beyond the Product Information:>
<Safety concern 2>	

V.2 Additional Risk Minimization Measures

V.3 Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
<Safety concern 1>	<Routine risk minimization measures:>	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:>

		<Additional pharmacovigilance activities:>
Safety concern	Risk minimization measures	Pharmacovigilance activities

Part VI: Summary of the risk management plan by product

This is a summary of the risk management plan (RMP) for <invented name>. The RMP details important risks of <invented name>, <how these risks can be minimised>, and how more information will be obtained about <invented name>'s risks and uncertainties (missing information).

<Invented name>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <invented name> shall be used.

VI.1 The medicine and what it is used for

<Invented name> is authorised for <indication outline – from Table Part I.1 – Indication(s)> (see SmPC for the full indication). It contains <INN> as the active substance and it is given by <route of administration – from Table Part I.1 "pharmaceutical form(s) and strengths">.

VI.2. Risks associated with the medicine and activities to minimize or further characterize the risks

VI.2.1. List of important risks and missing information

Important risks of <invented name> are risks that need special risk management activities to further investigate or minimize the risk, so that the pharmaceutical product can be safely <administered> <taken>. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <invented name>. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the pharmaceutical product that is currently missing and needs to be collected (e.g. on the long- term use of the medicine);

List of important risks and missing information (from Part II: Module SVIII)	
Important identified risks	<>
Important potential risks	<>
Missing information	<>

VI.2.2. Summary of important risks

<Important <identified> <potential> risk > or <Missing information>	
Evidence for linking the risk to the medicine	
Risk factors and risk groups	
Risk minimization measures	<Routine risk minimization measures> <Additional risk minimization measures> <No risk minimization measures>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <Short study name>

	See section VI.2.3 of this summary for an overview of the post-authorization development plan.

<Important <identified> <potential> risk 2> or <Missing information>	
Risk minimization measures	<Routine risk minimization measures> <Additional risk minimization measures>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <Short study name> See section VI.2.3 of this summary for an overview of the post-authorization development plan.

VI.2.3. Post-authorization development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

VI.2.3.2. Other studies in post-authorization development plan

Part VII: RMP Annexes

List of annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report s submission

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by EDA

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Annex 7 - Other supporting data (including referenced material

Annex 8 - Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change

Annex III.4. Templates: Cover page of Periodic Benefit Risk Evaluation Report (PBRER)

Periodic Benefit Risk Evaluation Report

for

ACTIVE SUBSTANCE(S): <INN>

ATC CODE(S): <Code(s)>

PHARMACEUTICAL PRODUCTS COVERED:

Invented name of the pharmaceutical product(s)	Marketing authorization number(s)	Date(s) of authorization *(Underline the International Birth Date)*	Marketing authorization holder
<>	<>	<>	<>
<>	<>	<>	<>

INTERNATIONAL BIRTH DATE (IBD): <Date>

EUROPEAN UNION REFERENCE DATE (EURD): <Date>

INTERVAL COVERED BY THIS REPORT:

From <date> to <date (i.e. data lock point)>

DATE OF THIS REPORT:

<Date>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

<E-mail address> **(contact person for the PBRER procedure)**

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>

Annex III.5. Templates: Direct healthcare-professional communication (DHPC)

<Date>

<Active substance, name of pharmaceutical product and main message *(e.g. introduction of a warning or a contraindication)***>**

Dear Healthcare professional,

<Name of marketing authorization holder> in agreement with General Administration for

Pharmaceutical Vigilance at the Egyptian Drug Authority would like to inform you of the following:

Summary

Style guide: This section shall be in larger font size than the other sections of the DHPC and preferably in bullet points.

<Brief description of the safety concern, recommendations for risk minimization *(e.g. contraindications, warnings, precautions of use)* and, if applicable, switch to alternative treatment>

<Recall information, if applicable, including level (pharmacy or patient) and date of recall>

<A statement indicating that the information is being sent in agreement with EDA, if applicable>

Further information on the safety concern and the recommendations

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors), also the reason for disseminating the DHPC at this point in time>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimization>

<Placing of the risk in the context of the benefit>

<A statement on any previous DHPCs related to the current safety concern that have recently been distributed>

<A schedule for follow-up action(s) by the marketing authorization holder/EDA, if applicable>

Further information

<Link/reference to other available relevant information, such as information on the website of EDA>

<Therapeutic indication of the pharmaceutical product, if not mentioned above>

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system>

<Mention if product is subject to additional monitoring and the reason why>

<Details *(e.g. name, postal address, fax number, website address)* on how to access the General Administration for Pharmaceutical Vigilance at the Egyptian Drug Authority spontaneous reporting system>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes

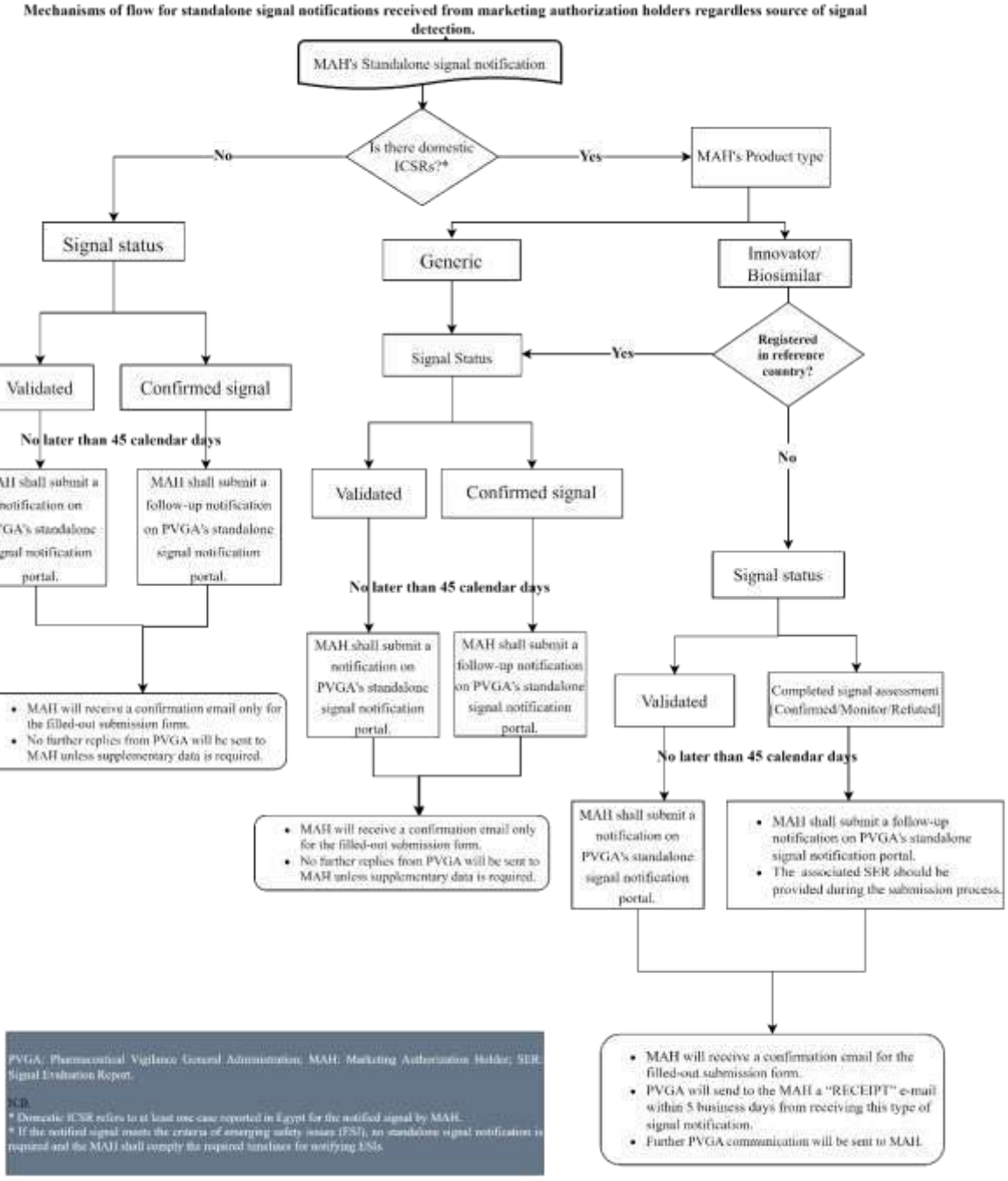
<Relevant sections of the Product Information that have been revised (with changes made visible)>

<Detailed scientific information, if necessary>

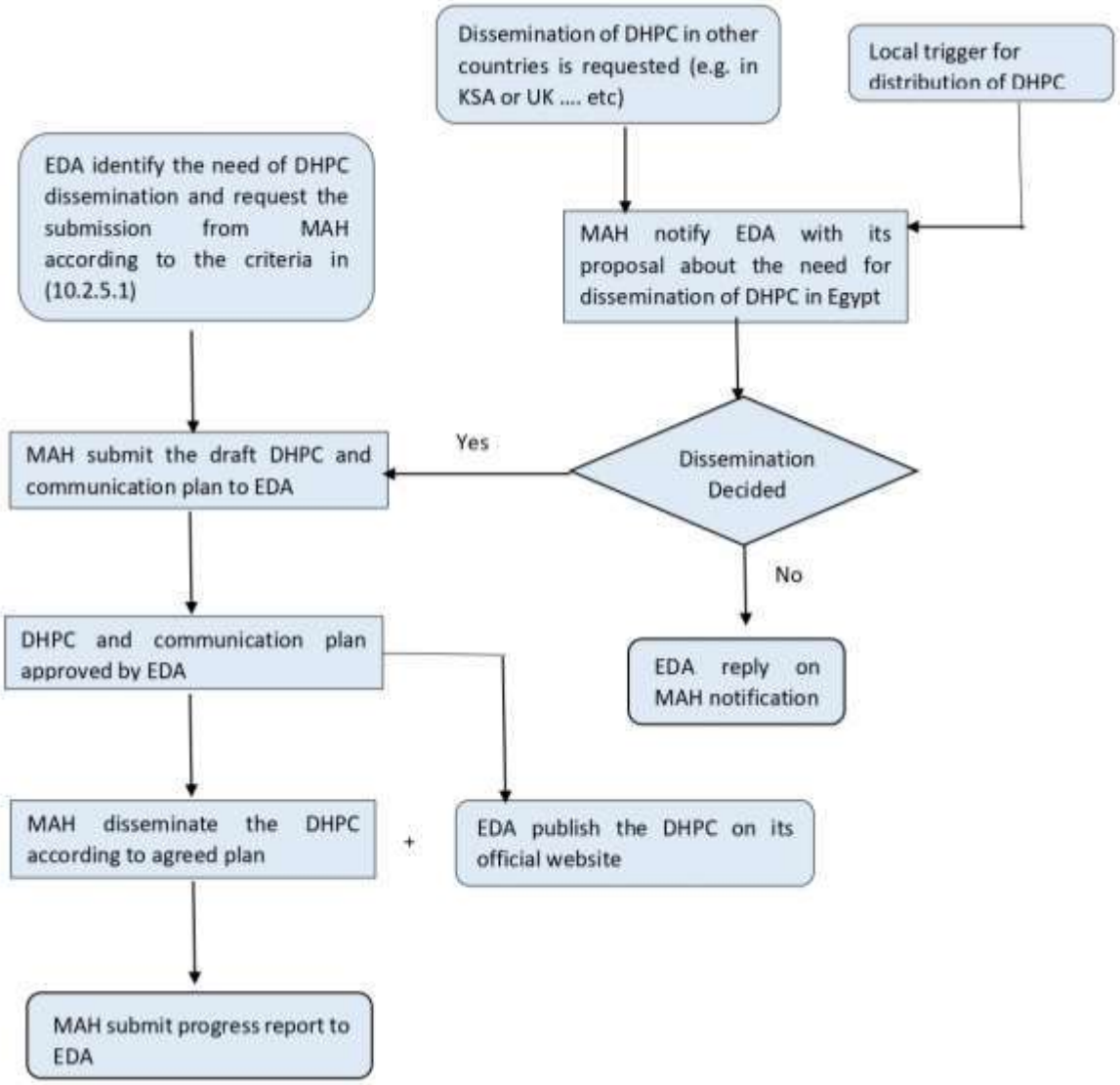
<List of literature references, if applicable>

17. Annex IV: Flowcharts

17.1. Flowchart for standalone signal notifications received from marketing authorization holders



17.2. Flowchart for safety communications



18. References:

1. Law No. 151/2019 for the establishment of EDA.
2. Assistant Ministerial Decree No. 2/2010 for the regulations of pharmacovigilance and pharmaceutical products safety.
3. Ministerial decree No. 368/2012 regarding the Egyptian pharmacovigilance center.
4. EDA chairman decree No. 382/2023 for the release of GVP Guideline in Egypt.
5. EDA chairman decree No. 92/2021 for the renewal of national pharmacovigilance committee and its amendments.
6. EDA chairman decree No. 184/2023 for implementation of the reliance system on the reference health regulatory authorities that approved by technical committee of drug control with regard to pharmacovigilance activities.
7. This Guideline is based on EMA guidelines for GVP, other resources were referenced as well, such as the ICH and the WHO for the GVP.
8. The Institute of Internal Auditors (IIA) www.theiia.org; the International Organization for Standardization (ISO) www.iso.org; Information Systems Audit and Control Association (ISACA) www.isaca.org; The International Auditing and Assurance Standards Board (IAASB) www.ifac.org; The International Organization of Supreme Audit Institutions (INTOSAI) www.issai.org.
9. International Auditing Standards: Issued by International Auditing Standardization Organizations.
10. International Auditing Standardization Organizations: More details regarding:
    - **The Institute of Internal Auditors** (IIA) standards can be found at http://www.theiia.org/guidance/standards-and guidance/ippf/standards/full-standards;
    - **The International Organization for Standardization (ISO)** standard 19011 "Guidelines for quality and/or environmental management systems auditing. http://www.iso.org/iso/home.html;
    - **Information Systems Audit and Control Association** (ISACA) standards can be found at http://www.isaca.org/Standards;
    - **The International Auditing and Assurance Standards Board** (IAASB) standards can be found at http://www.ifac.org/auditing-assurance/clarity-center/clarified-standards;
    - **The International Organization of Supreme Audit Institutions** (INTOSAI) can be found at http://www.issai.org/composite-347.htm.