Egyptian Drug Authority

Good Pharmacovigilance Practice

Guidelines in Egypt

For pharmaceutical products

Version 1	**GVP – Arab V.2**
Version 2	**Good Pharmacovigilance Practice Guidelines in Egypt - 2022**

Central Administration of Pharmaceutical Care

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 medicinal 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 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 adopting the European guidelines for good pharmacovigilance practices and adapts them to the Egyptian context, which is clearly explained in this document. The adoption of the European Medicines Authority Good Pharmacovigilance Practices (EMA GVP) as a base for this guideline does NOT undermine the right of EDA to have additional or sometimes changed requirements. Multinational marketing authorization holders should be attentive to these national requirements and bring the attention of their headquarters to them, consequently, take the necessary measure to comply. In this Guideline, all applicable legal requirements are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

For the operational procedures and communication with the 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.

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1 Pharmacovigilance systems and their quality systems

1.1 Introduction

This chapter provides 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 the Egyptian Drug Authority (EDA) to fulfill the tasks and responsibilities listed in this guideline and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance. The EDA likewise maintains a pharmacovigilance system to fulfill its pharmacovigilance activities.

For performing their pharmacovigilance activities, marketing authorization holders, and the EDA shall establish and use quality systems that are adequate and effective for this performance.

For more detailed guidance, refer to EMA GVP (module I - Pharmacovigilance systems and their quality systems

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

1.2 Structures and processes

The structures and the processes of pharmacovigilance in Egypt has to be implemented following the Good Pharmacovigilance practice. They can be achieved by having well-functioning pharmacovigilance system and a quality system for the pharmacovigilance, which are described in details in EMA GVP module I- Pharmacovigilance systems and their quality systems "I.B. Structures and processes''. This topic explains multiple items that shall be considered in implementation, such as Quality cycles, overall quality objectives for PV, principles for GVP, responsibilities for the quality system within an organization, training of personnel for PV, facilities and equipment for pharmacovigilance, specific quality system procedures and processes, including compliance managements by MAHs and EDA. In addition to record control, documentation of quality systems by MAHs and EDA, monitoring of the performance and the effectiveness of the PV system and its quality systems, and preparedness planning for PV in public health emergencies.

1.3 Operation of pharmacovigilance systems in Egypt

This topic explains the operations of pharmacovigilance systems in Egypt; identifying the roles and responsibilities of each of PV stakeholders concerned within the scope of this guideline. Additionally, the preparedness planning for PV in public health emergencies in Egypt.

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

For overall pharmacovigilance responsibilities of the applicant and marketing authorization holder in Egypt, they are responsible for the respective pharmacovigilance tasks and responsibilities in order to assure responsibility and liability for its authorized medicinal 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 medicinal 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 should conduct the pharmacovigilance tasks and responsibilities is provided in the respective GVP chapters.

For more details, refer to EMA GVP (module I- Pharmacovigilance systems and their quality systems "I.C.1. Overall pharmacovigilance responsibilities of the applicant and marketing authorization holder in the EU").

Special considerations in Egypt:

- **Responsibilities of the marketing authorization holder in relation to the qualified person responsible for pharmacovigilance**

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/ LSR – local safety responsible (at multinational companies) in Egypt. 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.

For multinational companies:

- A Local Safety Responsible (LSR) may be accepted in some Arab Countries; consult national medicines authorities for national requirements.
- In addition to the headquarter QPPV, the national medicines authorities request the nomination of a pharmacovigilance contact person (local safety responsible) in Egypt. Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. A contact person at national level may also be nominated as the Local Safety Responsible (LSR).

- **Qualifications of the qualified person responsible for pharmacovigilance.**

The marketing authorization holder shall ensure that the QPPV has acquired adequate theoretical and practical knowledge (e.g. pharmacovigilance methods, MedDRA coding, ICSRs processing activities , Evidence based medicine, How to conduct literature search, Causality assessment, Case Narrative Writing for Reporting Adverse Events, Pharmacovigilance quality management, Pharmacoepidemiology, Biostatistics, Signal detection, Medical Aspects of Adverse Drug Reactions, Risk benefit assessment, National pharmacovigilance regulations, Pharmacovigilance Planning and Risk Management Plans, Risk communication) for the performance of pharmacovigilance activities. The QPPVs should have a minimum of **Bachelor degree of pharmacy or medicine**, basic training in epidemiology and biostatics.

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 experience (Taking into consideration that pharmacovigilance practice and regulations are relatively new in Egypt and in the Arab Countries as well, thus having an experienced QPPV may be challenging. Accordingly, it is accepted in Egypt **for only a transitional period** that, 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 module II in pharmacovigilance.

All the above requirements are applied on the QPPV/LSR **and on all other members of the PV staff.**

- **Role of the qualified person responsible for pharmacovigilance**

The OPPV/ LSR is a natural person, as distinguished from a corporation which is often treated at law as a fictitious person.

The QPPV or the LSR shall acting as a single pharmacovigilance contact point for the national medicinal authority on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

The PV department shall be directly supervised by top management - CEO (i.e., directly report to the top management). It is accepted for the PV department to be supervised by medical department only if the medical department directly reports to the top management (CEO).

- **Specific quality system processes of the marketing authorization holder**

The retention of pharmacovigilance data and documents relating to patient (especially ICSRs, etc.) should be kept lifelong.

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

1. 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;
2. The terminology set out in EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated **medicinal product information'** (ISO/FDIS 11615:2012);
3. The terminology set out in EN ISO 11616:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated **pharmaceutical product information'** (ISO/FDIS 11616:2012);
4. The terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated **information on substances'** (ISO/FDIS 11238:2012);
5. The terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Medicinal 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).
6. The terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of **units of measurement** '(ISO/FDIS 11240:2012).

- **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 party i.e. **another organization**, "**not individuals**, **the freelance person is not applicable in Egypt**.

1.3.2. Overall pharmacovigilance responsibilities regulatory authority in Egypt

The national medicine authority (EDA) in Egypt is responsible for the respective pharmacovigilance tasks and responsibilities in order to ensure that appropriate actions can be taken, when necessary. For this purpose, the 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

The EDA must operate a pharmacovigilance system [through its PV general administration/Egyptian center for PV] for the fulfilment of their pharmacovigilance tasks. In this context, the EDA is responsible for the safety monitoring of each medicinal 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 this guideline.

The EDA should 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 Pharmacovigilance advisory committee is to provide advice on the safety of medicinal products for human use and the investigation of adverse reactions, in order to enable effective risk identification, assessment and management, in the pre- and post-authorization phase leading to recommendations on action at the request of the pharmaceutical vigilance general administration for products available in Egypt. The roles and responsibilities of the Pharmacovigilance Advisory Committee include, but not limited, to the following:

1. Evaluation of potential signals arising from spontaneous reporting, including those identified from the National Pharmacovigilance and Safety reports database, and all other sources.
2. Investigation of adverse reactions.
3. Regularly review Drug monitor of safety concerns.
4. Discussion of emerging safety concerns at the request of the National Pharmacovigilance and Drug Safety Center / Directorate (NPC).
5. Discussion of PBRERs at the request of the NPC.
6. 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 systems of EDA in Egypt

EDA has to establish a quality system capable of maintaining specific quality system processes as described in (1.2 structures and processes). For more guidance, refer to EMA GVP (module I - Pharmacovigilance systems and their quality systems “I.C.2.4. Specific quality system processes of the quality systems of competent authorities in Member States and the Agency”).

The used terminologies are referred to (Specific quality system processes of the marketing authorization holder in Egypt - Special considerations in Egypt - Use of internationally agreed terminology).

1.3.3. Preparedness planning for pharmacovigilance in public health emergencies in Egypt

The pharmacovigilance systems of marketing authorization holders and the EDA should be adaptable to public health emergencies. Preparedness plans should be developed as appropriate

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

2 Pharmacovigilance Master File

2.1 Introduction

There are legal requirements for marketing authorization holders to maintain and make available upon request a pharmacovigilance system master file (PSMF) to the EDA.

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 medicinal products.

For more detailed guidance, refer to EMA GVP (Module II -Pharmacovigilance system master file).

Special considerations in Egypt:

- **The multinational MAHs/applicants in Egypt:**

All MAHs must 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 should reflect global availability of safety information for medicinal products authorized for the MAH, with information on the pharmacovigilance system to the local or regional activities. The Multinational MAHs/Applicants should 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):

1. **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 module apply to the PSMF of the multinational MAH/applicant), and
2. **National Pharmacovigilance Sub-System file (National PSSF)** which describes the key elements of pharmacovigilance activities in Egypt.

2.2 Structures and processes

The PSMF is a legal requirement in Egypt. This topic concerns the requirements for the PSMF and is applicable for any medicinal product authorized in Egypt, irrespective of the marketing authorization procedure. The required content and management of the PSMF 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 PSMF should reflect global availability of safety information for medicinal products authorized in Egypt, presenting information on the pharmacovigilance system applied at global, regional and local levels.

For more detailed guidance, refer to EMA GVP (Module II -Pharmacovigilance system master file "II.B. Structures and processes").

Special considerations in Egypt:

- **The summary of the applicant's pharmacovigilance system:**

Except in the situations described in the accessibility of PSMF, where the full PSMF (along together with its summary) is requested to be submitted in the marketing authorization application; only a summary of the applicant's pharmacovigilance system is required to be included in the marketing authorization application, 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) and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil on the national level the pharmacovigilance tasks and responsibilities listed in this GVP modules.*

For multinational MAHs/ applicants, the Summary of the national pharmacovigilance system/sub-system should include the above-clarified information as for PSMF.

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

- **The location, registration and maintenance:**

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 should 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 the national medicinal authority (EDA) at any time.
- The local office/ affiliate of the MAH/applicant has detailed description on the pharmacovigilance system/ activities on the local level.

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

- **PSMF section on qualified person responsible for pharmacovigilance (QPPV):**

Special considerations applied on Egypt's PV staff (QPPV/LSR – PV responsible person for the multinational companies in Egypt- and other PV staff):

A checklist on the following required practical experience/ trainings shall be provided. Taking into consideration that pharmacovigilance practice and regulations are relatively new in Egypt, thus having an experienced QPPV/LSR & PV staff may be challenging. Accordingly, it is accepted by the national medicinal authority (EDA) in Egypt **that for only a transitional period** the QPPV/LSR & PV staff qualification may be expressed in terms of his pharmacovigilance training rather than his practical experience in pharmacovigilance. Under these circumstances, once the QPPV/ QPPV/LSR & PV staff are appointed, the MAH is responsible of providing him the unachieved trainings in light of the checklist below. (Consult with national medicines authority in Egypt for transitional period duration & conditions, if any,).

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***

- **PSMF section on pharmacovigilance processes:**

The process description must be combined with **list** of the following **processes for compliance management**, as well as interfaces with other functions:

1. 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;
2. The scientific evaluation by the marketing authorization holder of all information on the risks of medicinal products.
3. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the national medicines authority within the time limits provided in the national regulations.
4. The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signal.
5. Effective communication by the marketing authorization holder with the national medicinal authority, including communication on new risks or changed risks, the pharmacovigilance.
6. System master file, risk management systems, risk minimization measures, periodic safety.
7. Update reports, corrective and preventive actions, and post-authorization studies.
8. 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 the national medicinal authority.
9. Appropriate communication by the marketing authorization holder of relevant safety information to healthcare professionals and patients.

- **PSMF section on pharmacovigilance system performance:**

The accepted target is not less than 90%, and it is expected to be improved by time.

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

- **PSMF section on quality system:**

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

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

- **Annex to PSMF:**

In addition to the list of contractual agreements covering delegated activities, a copy of the individual contractual agreements shall also be included in this annex when the PSMF is submitted to the national medicinal authority.

- **Change control, logbook, versions and archiving by the multinational MAHs/ applicants:**

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

1. **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 module apply to the PSMF of the multinational MAH/applicant), and
2. **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 have 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).

- **Pharmacovigilance system master file presentation:**

The provision of the document shall be within 14 days of request by the EDA (unless otherwise stated in the request).

- **Format and layout:**

1. Cover Page: should also include, (company profile number, and commercial registry number).
2. Annex A: should also include,
    a. All documents for qualification and experience evidences.

b. All requirements are required for all PV staff.

3. Annex B: should also include.
   a. Official organogram(s).
   b. Copies of PV agreement(s)/ PV related agreements.
4. Annex C: should also include, **Flow diagrams** to indicate the main stages, timeframes and parties involved in safety data collection and its outcome.
5. Annex E: should also include, all applied procedures guidance e.g., Stander operating procedures (SOPs), work instructions (WIs)…etc.
6. The 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

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

For more detailed guidance, refer to EMA GVP (Module II -Pharmacovigilance system master file "II.C.1and II.C.II)

Special considerations in Egypt:

- **The responsibilities of MAHs/applicants:**

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 the national medicines authorities as applicable.

- **The responsibilities of EDA:**

The EDA will review the summary information about the pharmacovigilance system, and full PSMF as appropriate, included in the marketing authorization application.

The EDA should manage the 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/ PV staffs contact information and the products relevant to the pharmacovigilance system described in the pharmacovigilance system master file.

- **The accessibility of PSMF:**

The marketing authorization holder shall maintain and make available on request a copy of the pharmacovigilance system master file. The marketing authorization holder must submit the copy within 14 days after receipt of the request from the national medicinal authority (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:

1. The applicant has not previously held a marketing authorization Egypt, the full PSMF is appropriate to review the description of a pharmacovigilance system.
2. The applicant has not previously submitted the PSMF in Egypt or it is in the process of establishing a new pharmacovigilance system.
3. The applicant had major changes in its organization, such as mergers, acquisitions, splitting, and separation or in its pharmacovigilance system.
4. The applicant has major or critical findings in the previous pharmacovigilance system assessment by the national medicinal authority.

5. 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
6. 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 inspection module).
7. Where specific concerns about the pharmacovigilance system and/or the product safety profile exist.
8. Any other situation as seen appropriate by the national medicinal authority.

Except in the above situations, the pharmacovigilance system master file should 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:

1. Particularly if a new pharmacovigilance system is being implemented or the MAH has not previously submit the PSMF and the national PSSF in Egypt; or
2. If product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified; or
3. In preparation for a pharmacovigilance inspection.
4. Any time upon request of the national medicinal authority.

For multinational MAHs/ applicants:

1. The PSMF and the national PSSF shall be maintained in a current state and be permanently available to be submitted.
2. 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.
3. Except in the above situations, the PSMF and/or the national PSSF (as appropriate) should 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" should be submitted. The following table summarizes the different scenarios:

Conditions	**Document submitted**
Situations in 2.3.2. apply to both PSMF and the national PSSF	PSMF & summary PSMF National PSSF & summary of national PSSF
Situations in 2.3.2. apply to only national PSSF	Summary PSMF & National PSSF & summary of national PSSF
Situations in 2.3.2. apply to only PSMF	PSMF & summary PSMF summary of national PSSF
Situations in 2.3.2. do NOT apply to both PSMF and the national PSSF	Summary PSMF & summary National PSSF

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.

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.

In order to determine the marketing authorization holders' compliance with pharmacovigilance obligations established within Egypt, and to facilitate compliance and improvement processes, the 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 the 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 their activities.

For detailed guidance, refer to EMA GVP (Module III Pharmacovigilance inspections).

3.2 Structures and processes

The structures and the processes of pharmacovigilance inspections in Egypt has to be implemented following the Good Pharmacovigilance practice. This topic explains multiple items that shall be considered in implementation such as: Inspection types, inspection planning, sites to be inspected, inspection scope, inspection process, inspection follow-up, regulatory actions and sanctions, record management and archiving, qualifications and training of inspectors, and quality management of PV inspection process.

Special considerations in Egypt:

- **Inspection process:**

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

- **Inspection follow-up:**

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.

3.3 Operation of pharmacovigilance inspections 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.

For more detailed guidance, refer to EMA GVP (Module III -Pharmacovigilance inspections, III.C)

3.3.1. Role of the EDA

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

Pharmacovigilance inspections should 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 roles of MAHs/applicants for inspection in Egypt.

3.3.2. Role of MAHs/applicants

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

1. Always to be inspection-ready as inspections may be unannounced.
2. 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.
3. 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.
4. 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
5. 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.

Special considerations in Egypt:

- **Inspection programs:**

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.

Note:

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.

4 Pharmacovigilance Audit

4.1 Introduction

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 and support a risk-based approach to pharmacovigilance audits.

For detailed guidance, refer to EMA GVP (Module IV Pharmacovigilance audits)

For different terminologies, refer to terminology 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. 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.

Special considerations in Egypt

- **Risk-based approach to pharmacovigilance audits:**

Regarding the findings: kindly refer to (3.3. Operation of pharmacovigilance inspections in Egypt) in this guideline.

- **Quality system and record management practices:**

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization (i.e. within the national medicines authority 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.

4.3 Operation in Egypt: Pharmacovigilance audit policy framework

This section describes the pharmacovigilance audit policy framework and organizational structure in Egypt. It defines the roles and the responsibilities of PV stakeholders concerned with this guideline regarding auditing, reporting, and keeping confidentiality.

For more detailed guidance, refer to EMA GVP (Module III -Pharmacovigilance Audits IV.C)

Special considerations in Egypt

- **Qualified person responsible for pharmacovigilance (QPPV)/LSR:**

For multinational MAH; the local safety responsible (LSR) in Egypt where the audit to be conducted should 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 should be notified of any audit findings relevant to the pharmacovigilance system in where the audit was conducted.

- **Confidentiality:**

Documents and information collected by the internal auditor should 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 Plan (RMP)

5.1 Introduction

A medicinal 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 medicinal 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 medicinal product's important risks. To this end, the RMP contains:

1. The identification or characterization of the safety profile of the medicinal 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).
2. The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions (the pharmacovigilance plan).
3. 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 medicinal product's safety profile increases over time, so will the risk management plan change.

Terminology

Identified risk

An untoward occurrence for which there is *adequate evidence of an association with the medicinal 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.

Potential risk

An untoward occurrence for which there is **some basis for suspicion of an association with the medicinal 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 medicinal product.

Missing information

Gaps in knowledge about the safety of a medicinal 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 should 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.

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*.

Notes:

The RMP should 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 medicinal 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 should be considered a potential risk, and if deemed important, should 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.

Risk management system

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

Risk management plan

A detailed description of the risk management system.

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.

Safety concern

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

Target population (treatment)

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information.

5.2 Structures and processes

Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular medicinal 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 medicinal product's life cycle. The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorization safety data.

The RMP is a dynamic document that should 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.

With the exception of some patient registries, it is expected that over time the additional pharmacovigilance activities in the RMP will be completed and thus removed from the RMP.

For more details, Guidance on templates of RMPs refer to EU GVP Module V.

Special considerations in Egypt:

- **Responsibilities for risk management**

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

Marketing authorization holders and applicants

In relation to risk management of its medicinal products, an applicant/marketing authorization holder is responsible for having an appropriate risk management system in place and ensuring that the knowledge and understanding on the product's safety profile, following its use in clinical practice, are critically reviewed. The marketing authorization holder should monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products, and update the risk management system and the RMP accordingly.

EDA

In relation to risk management, the principal responsibilities of medicines authorities are constantly monitoring the benefits and risks of medicinal 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 medicinal product including ensuring the accuracy and completeness of all information produced by the company in relation to its medicinal 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 medicinal products make similar changes to their risk minimization measures when changes are made to those of reference medicinal product.

- **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 [For RMP template, refer to EU GVP module V]. Part II of the RMP - Safety specification is subdivided into modules, so the content can be tailored to the specifics of the medicinal 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 modules may have reduced content requirements. However, the RMP document is expected to be submitted as one single document including all modules 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 EU 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

For further details and the description of the content of all parts and modules and Annexes, refer to EU GVP Module V.

The RMP is part of the scientific dossier of a product and as such should be scientifically based and should not include any element of a promotional nature.

The Pharmacovigilance activities

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

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

For more details on the routine and additional pharmacovigilance activities, refer to EU GVP Module V.

- **Routine pharmacovigilance activities**

Routine pharmacovigilance is the primary/minimum set of activities required for all medicinal products and should 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 should 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 should 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.

For more details on the routine pharmacovigilance activities, refer to EU GVP Module V.

- **Additional pharmacovigilance activities**

The applicant/marketing authorization holder should 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 medicinal product. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a Egyptian drug authority (EDA) should 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 should relate to the safety concerns identified in the safety specification, be feasible and should not include any element of a promotional nature.**

- **The risk minimization measures**

The RMP should 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 should adverse reactions occur. Planning and implementing risk minimization measures and assessing their effectiveness are key elements of risk management.

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

Safety concerns of a medicinal 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 medicinal product.

For more details on the risk minimization measures, refer to EU GVP Module V & Module XVI

- **Routine risk minimization activities**

Routine risk minimization activities are those which apply to every medicinal 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 medicinal product.

MAH should 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 medicinal 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" should 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 medicinal 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 medicinal product may be prescribed, or the conditions under which a patient may receive a medicinal product.

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

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

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

For more details on the routine risk minimization, refer to EMA GVP Module **V**

- **Additional risk minimization activities**

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

Any educational material should be non-promotional and any educational program should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programs should 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 carers)
- 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** should be submitted to Pharmaceutical Vigilance General Administration (PVGA) - **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 should be submitted (through pv.compliance@edaegypt.gov.eg) (Affirming the complete distribution of the DHPC to all HCPs included in the list).

- **Educational material**

Any educational material should **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 should 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 should be prepared and submitted in "***Arabic*** ".

The Educational material **content and the distribution details** should 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 should be submitted (through pv.compliance@edaegypt.gov.eg) (Affirming the complete distribution of the Educational material).

For more details and further guidance on additional risk minimization measures is provided in EU GVP Module XVI.

- **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 should be performed for the additional risk minimization tools individually and for the risk minimization program as a whole.

Effectiveness evaluation should 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 should be considered, process indicators and outcome indicators.

If a study to evaluate the effectiveness of risk minimization activities is required, the study should 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 EU GVP Module XVI.

- **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 should 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 should apply the quality principles. The marketing authorization holder should maintain records of when RMPs were submitted to Medicines authorities 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 of risk management

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 medicinal product (or a series of medicinal 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 medicinal 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 should be included in one RMP unless separate presentations are requested by the Egyptian Drug Authority (EDA) or agreed by the same at the request of the applicant/marketing authorization holder.

Special considerations in Egypt:

- **Implementation of additional risk minimization activities**

For products with additional risk minimization activities, it is the responsibility of the marketing authorization holder and the Egyptian Drug Authority (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 should 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:

1. safety concerns relating to the active substance;
2. safety concerns related to a specific formulation or route of administration;
3. safety concerns relating to the target population;
4. risks associated with switch to non-prescription status.

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

- **Justification for not submitting RMP**

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

Clear statement that the innovator 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 should 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.

- **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 medicinal 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 medicinal 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 should 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:

1. To highlight to what extent the risk management activities proposed to be implemented nationally adhere to the globally implemented plan and;
2. To provide justification for any difference (apart from what implemented in the EU/Globally) whenever exist including the needed national tailoring if any.
3. In addition it should 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.
4. It provides good evidence that the LSR/QPPV has clear understanding and commitment about the activities that will be implemented on the national level and how they will be implemented.

Note:

In case the EU/Global RMP is available, an Egyptian display of EU/Global RMP **should be also submitted**

In case no EU/Global RMP available, a globally signed declaration declaring that **should be submitted**.

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

- **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 should 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 medicinal product where such use is outside the terms of the marketing authorization.

This Addendum should be signed and accompanied by the CV of the expert. The clinical expert should have the necessary technical or professional qualifications and may, but should not necessarily, be the same qualified person responsible for pharmacovigilance.

The Addendum to the Clinical Overview should 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 medicinal 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 medicinal 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)" should 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 should 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 medicinal product considered relevant for the implementation of the safety data, a brief description should be provided; such patterns may include in particular off-label use

sub-section “Cumulative and interval patient exposure from marketing experience” should include an estimate patient exposure, an estimate of the number of patients exposed should 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” should 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 should be clarified.**

MAHs should 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 should 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 medicinal product & include summary of literature articles highlighting only the significant data along with the company’s comment on each Literature case. The full articles should be annexed.

Section titled "Risk evaluation": subsection titled "Characterization of risks": should 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 should 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 should be presented, based on the above information.

Section titled “Late-breaking information” should 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 should be signed & accompanied by CV of the expert and should:

1. Confirm that no new clinical data are available which change or result in a new risk-benefit evaluation.

2. 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 should be specified and justified.
3. Confirm that the authorities have been kept informed of any additional data significant for the assessment of the benefit/risk ration of the product concerned.
4. 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 should be submitted.
- The ACO document should be signed by the QPPV.
- The period covered by the ACO should 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)

  Note: In case of the biological products, the ACO should cover 5 years.
- The stamped approved label should 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 **should 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 should 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.

General comments

- The RMP is part of the scientific dossier of a product and as such should be scientifically based and should not include any element of a promotional nature.
- Any educational program should be completely separated from promotional activities and contact information of physicians or patients gathered through educational program should not be used for promotional activities.
- Regular monitoring of the activities of the medicinal 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 should 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 should be signed by the qualified person for pharmacovigilance (QPPV).
- In case of a non-reference product, MAH should 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 & 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 & 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 should be submitted and the following parts: **Part I, Part VI** & **Annex 3** should separately represent data of each product (repeated for each medicinal product/concentration).
- The product leaflet should 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 medicinal 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*".

  For more detailed guidance, refer to the EMA GVP Module X – Additional monitoring and any further updates.
- **All reference documents used to prepare RMP should 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 , for example –but not restricted to-:
    - Public assessment report
    - The SmPC of the reference product
    - Search results

Routine RMP

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.

In addition, situations when a risk management plan should be submitted:

1. With an application involving a significant change to an existing marketing authorization:
2. New dosage form;
3. New route of administration;
4. New manufacturing process of a biotechnologically-derived product;
5. Pediatric indication;
6. Other significant change in indication;
    - A significant change in indication is a change of authorized indication(s) of a medicinal product where the new treatment target population differs materially from the one for which the medicinal 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.
7. At the request of the national medicines authority when there is a concern about a risk affecting the risk-benefit balance;
8. With a submission of final study results impacting the RMP;
9. With a PBRER for medicinal product, when the changes to the RMP are a direct result of data presented in the PBRER.

The need for a RMP or an update to the RMP should be discussed with the EDA, as appropriate, well in advance of the submission of an application involving a significant change to an existing marketing authorization.

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

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 medicinal product that occur in a single patient at a specific point of time.

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

Marketing authorization holders should report ICSRs to the General Administration of Pharmaceutical Vigilance at the Egyptian Drug Authority.

For more detailed guidance, refer to EMA GVP module VI.

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.

For more detailed guidance and submission modalities, refer to EMA GVP module VI – VI.B

Special considerations in Egypt

- **Collection of ICSRs:**

Marketing authorization holders should collect reports originating from unsolicited or solicited sources.

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

- **Validation of ICSRs:**

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

1. One or more identifiable reporter (all parties providing case information or approached for case information should be recorded in the ICSR- not only the initial reporter).
2. One single identifiable patient (characterized by at least one of the following qualifying descriptors: initials, medical record number {from a general practitioner, specialist, hospital, or investigation}, date of birth, age, age group, gestation period, or gender). **N.B.** In Egypt, the patient identifier is not considered a confidential data.
3. One or more suspected substance/medicinal product (Interacting substances or medicinal products should also be considered suspected)
4. One or more suspected adverse reactions **N.B.** The report 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.

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

In addition to the previous mandatory elements, an ICSR should 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**

In Egypt, all the submitted ICSRs shall be provided with a detailed case narrative containing all detailed information (as events, drug names, dates, diagnosis) 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.

- **Submission 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 should 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 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

Electronic transmission of individual case safety reports should be implemented with Medical Dictionary for Regulatory Activities (MedDRA) coding.

MedDRA coding should be used at the lowest level term (LLT).

When MedDRA terms are used, the MedDRA version number should be provided.

- **Reception of ICSRs:**

Pharmaceutical companies should 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.

ICSRs Reception Technical Fields

List of fields	Field type	Mandatory	Format
Submission date	Auto generated	Yes	--
Company name	Auto filled	Yes	--
Initial report date	Text	Yes	dd/mm/yyyy

(Day zero*)			
Seriousness	Radio button with answers: yes or no	Yes	
Case ID	Text	Yes	
Product name	Text	No	
Report type	Radio button with answers: Initial or Follow up	Yes	
ICSR file (attachment)	Attachment	Yes	XML format CIOMs form (pdf)

Seriousness criteria

A serious adverse event or reaction is any untoward medical occurrence associated with the use of a medicinal product in a patient, that at any dose the patient outcome is one of the following:

1. Death
2. Life-Threatening
3. Hospitalization (initial or prolonged)
4. Disability
5. Congenital Anomaly
6. Medically important event or reaction
7. The characteristics/consequences should be considered at the time of the reaction to determine the seriousness of a case.

- **Time frame for reporting**

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 should 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 should be followed and MAHs should adhere to the specified time frame. As in case of reporting of vaccines under "Emergency Use Authorization (EUA)": Pharmaceutical companies should collect and report 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

- **Follow-up of reports**

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should 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, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information.

Significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case, or could change its seriousness criteria. Non-significant information includes updated comments on the case assessment, or corrections of typographical errors in the previous case version.

Any attempt to collect missing data elements and obtain follow-up information should be documented.

Examples on important data elements that may need Follow-up:

a- Patient's age:

The patient's age is important in order to be able to identify safety issues occurring specifically in the pediatric or elderly population. Reasonable efforts should be made to follow-up on ICSRs where information on the patient's age or age group is initially not reported by the primary source

b- Data related to biological medicinal products:

For suspected adverse reactions related to biological medicinal products, the definite identification of the concerned products with regard to their manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the names of the products and their batch numbers.

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.

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 competent authorities and are further sent as attachments in line with ICH E2B(R3). These submissions are considered as amendment reports.

Report nullification

The nullification of ICSRs should be used to indicate that a previously transmitted report should 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.

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

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

Special situations

Use of a medicinal product during pregnancy or breastfeeding

These cases should 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 medicinal 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 should 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 medicinal product, should 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 should reflect the mother’s characteristics; information regarding the father should 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, should be created.

Both reports should 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.

Only a parent report should be created to describe the child exposure to the medicinal product.

The patient characteristics refer only to the parent (mother or father) who may as well experience adverse reactions with the suspected medicinal product.

Reports with no reaction should not be submitted as ICSRs.

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 medicinal product was taken by the father, this information should also be recorded.

Important Notes:

- **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).

- **Diagnosis / Signs and Symptoms**

If a diagnosis is reported with characteristic signs and symptoms, the preferred option is to select a term for the diagnosis only and to MedDRA code it. If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA-coded.

- **Causality assessment**

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

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

For further information regarding ICSRs reporting, refer to EMA Guidelines Module VI and its addendum I.

Definitions

What is Day Zero?

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.

What is 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>.

What is 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).

What is 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.

6.3 Operation of ICSR 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 medicinal products for human use authorized in Egypt, independently of their condition of use.

For detailed guidance on interface with clinical trials and post authorization safety studies, collection of ICSR, responsibilities of MAHs concerned with this guideline, electronic submission of individual case safety reports, and submission modalities, refer to EMA Guidelines Module VI.C

Special consideration in Egypt:

- **EDA roles and responsibilities:**

1. 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, the 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 should be applied to those reports.

2. Pharmacovigilance data and documents relating to individual authorized medicinal products shall be retained as long as the product is authorized and for at least 10 years after the marketing authorization has expired. However, the documents shall be retained for a longer period where national law so requires.
3. EDA shall take all appropriate measures to encourage healthcare professionals and consumers to report suspected adverse reactions.
4. 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 medicinal 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.
5. EDA shall develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and consumers in order to collect -across the Country- harmonized information relevant for the evaluation of suspected adverse reactions, including errors associated with the use of medicinal products. In this context, core data fields for reporting will be made available for use in its national reporting systems as applicable.
6. The reports of suspected adverse reactions received from healthcare professionals and consumers should be acknowledged where appropriate and further information should be provided to the reporters as requested and when available.
7. If there are justifiable grounds resulting from pharmacovigilance activities on the national level, EDA may impose additional obligations on marketing authorization holders for the reporting of suspected adverse reactions.
8. 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 national pharmacovigilance center as appropriate.

- **Electronic exchange of safety information:**

For the classification, description, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, EDA and marketing authorization holders shall apply the hereafter "internationally agreed terminology" and "internationally agreed formats and standards".

Use of internationally agreed terminology

a. ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA);

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

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

d. the terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on substances‘ (ISO/FDIS 11238:2012);

e. the terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Medicinal 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);

f. the terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Medicinal 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

1. 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;

2. ICH M2 standard _Electronic Transmission of Individual Case Safety Reports Message Specification‘.

3. 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);

4. EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated medicinal product information‘ (ISO/FDIS 11615:2012);

5. EN ISO 11616:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard Data elements and structures for unique identification and exchange of regulated pharmaceutical product information‘ (ISO/FDIS 11616:2012);

6. EN ISO 11238:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, _Data elements and structures for unique identification and exchange of regulated information on substances‘ (ISO/FDIS 11238:2012);

7. EN ISO 11239:2012, Health Informatics, Identification of Medicinal 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);

8. EN ISO 11240:2012, Health Informatics, Identification of Medicinal 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 should be applied:

1. MedDRA Term Selection: Points to Consider Document - The latest version of the
2. ICH-endorsed Guide for MedDRA Users;
3. ICH E2B (R5) Implementation Working Group - Questions & Answers (March 3, 2005);
4. 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 should 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 (PSURs), are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.

This chapter discusses guidance on the preparation, submission and assessment of PBRERs.

For detailed guidance, refer to EMA GVP Module VII.

7.2 Structures and processes

This section provides guidance on the scope, objectives, format and content of PBRER. For detailed guidance on objectives of PBRER, principles for evaluation of the risk-benefit balance and scope of information to be included, principles for the preparation of PBRER, reference information, the format and content of PBRER, quality systems for PBRERs, and training of staff members related to PBRER, refer to EMA GVP module VII.B.

The main objective of a PBRER/PBRER is to present a comprehensive, concise, and critical analysis of risk-benefit balance of the medicinal 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 authorization evaluation at defined time points in the lifecycle of a product.

The PBRER format described in the ICH-E2C (R2) guideline replaces the PBRER format previously described in the ICH-E2C (R1).

7.3 Operation in Egypt

This subsection discusses the routine submission of PBRER, PBRER submission on demand by EDA, timelines for submission, process for PBRER assessment, Egyptian appendix requirements, quality system and record management, and renewal of marketing authorizations. For detailed guidance refer to EMA GVP module VII.C

Special consideration in Egypt:

- **Submission of PBRER:**

The PBRERs are submitted according to the list of EU reference dates (EURD list) *(MAHs must follow the dates and frequency stated in the most updated version of this list)

For active substances and combinations of active substances not included in the EURD, the MAH should check the supplementary list published on EDA's website.

For active substances/combinations not included, the MAH should the submit a request to the Pharmaceutical Vigilance General Administration to define frequency.

Each marketing authorization holder (MAH) shall be responsible for submitting PBRERs for all its own products once a license is granted according to the following timelines:

A. *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)

B. *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 the EDA): the timeline for the submission will be specified in the request; otherwise, the ad hoc PBRERs should be submitted within 90 calendar days of the data lock point.

The stated above submission timelines must not be exceeded otherwise this will be considered a deviation / non-compliance.

In case of submitting PBRERs of not marketed products, such information should be supported by a statement signed (on MAH official paper) by the CEO declaring that your product is not launched yet, never been marketed or sold by any tenders along with adequate justification & that the company will inform us once the product is marketed.

* **EURD list**: a comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different marketing authorizations, together with the corresponding EU reference dates, **frequencies for submission of periodic safety update reports and related data lock points**", it is updated every month & published on the European Medicines Agency website. The list enables the harmonization of PBRER submissions for medicinal products containing the same active substance or the same combination of active substances. A single PBRER assessment provides a mechanism for evaluating the totality of available data on the benefits and risks of an active substance or combination of active substances. This single assessment on the national level is important in avoiding duplication of efforts and in prioritizing the use of limited resources.

Why PBRER is needed[2]

As Clinical trial safety data limited: small number of patients, exclusion of at risk/special population groups, short duration, tightly controlled doses & closely monitored patients. Thus, at the time of approval, ADRs (especially rare & delayed onset ADRs), drug interactions & issues related to real world use of the drug are not known & continuous surveillance & analysis of risks in context of benefits is vital in post marketing phase.

PBRER ensures <u>continuous evaluation of the benefit risk</u> of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits to promote and protect public health and to enhance patient safety through effective risk minimization.

- **<u>PBRER should:</u>**

Be a **single document** for an active substance (including information on all approved indications, dosage forms & regimens), unless **otherwise** stated by the EURD list or requested by the EDA.

Be a **stand–alone document** for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, **are not to be accepted**.

Be a **global pharmacovigilance document** (worldwide information and same format & content) hence, the same PBRER is submitted to several authorities worldwide.

Include **benefit** data related **only** to use in **approved indications**, but include **all types of data on safety and risk regardless of indication**.

Include and **discuss new** information in a level of detail proportionate to its **potential impact on the benefit-risk profile.**

- **<u>PBRER should NOT be:</u>**

The means or channel to **provide initial notification of significant new safety information or efficacy information**.

Used as a mean to **detect new safety concerns or issues**. MAH should perform regular signal detection activities and literature monitoring to detect new safety concern.

- **PBRER content:**

When preparing the PBRER, the ICH-E2C(R2) guideline on PBRER should be applied. Guidance on the titles, order and content of the PBRER sections is provided in VII.B.5.1. to VII.B.5.21. of the EMA GVP module VII.B.

When no relevant information is available for any of the sections, this should be stated under the section, but do NOT omit any section.

Notes for some sections:

1- **Actions taken in the reporting interval for safety reasons:**

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 **national medicines authorities**.

If known, the **reason** for each action should be provided and any additional relevant information should be included as appropriate.

Relevant updates to previous actions should also be summarized in this section.

2- **Estimated Exposure, use patterns and summary tabulations:**
   - Estimated exposure:

Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD.

Separate estimates should be provided for **cumulative exposure** (since the IBD), when possible, and **interval exposure** (since the data lock point of the previous PBRER) from marketing experience, along with the **method used to determine the estimation.** In addition, the data should be routinely presented by sex, age, indication, dose, formulation, and region, **where applicable**.

The MAH should compare the patient exposure during current and previous reporting intervals and explain reasons in case of an increase of AE reports while there is a decrease in patient exposure.

   - Use patterns:

Where post-authorization use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include non-interventional studies designed to obtain this information, including registries. Other sources of information may include 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).**

If the marketing authorization holder becomes aware of a pattern of use of the medicinal product, the MAH should provide a brief description of it. **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 anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches).**

- Summary tabulations:

As 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)** should be presented in the summary tabulations.

The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A.

PBRER should present cumulative summary tabulations of SAEs from clinical trials & post-marketing sources that have been reported to the MAH since the DIBD.

The following AEs are **included**:	The following AEs are **not included**:
All SAEs from interventional clinical trials All spontaneous AEs (including literature) All serious related AEs from solicited sources	Non serious AEs from interventional clinical trials Solicited sources: Serious + unrelated All non-serious event

Whether to use PBRER qualifying cases or all cases when discussing a safety topic is depending on the topics:

For update or new information of a previously discussed topic: can be based on PBRER qualifying cases

For new topics or product use in special population advice to use all cumulative cases or all cases received during the reporting interval.

S*ummary tabulation should be reviewed in the context of exposure.*

3- Overview of signals: new, ongoing, or closed:

MAH should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should 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;
- Brief summary of the key data;
- Plans for further evaluation; and
- Actions taken or planned.

The methods of signal detection can be:

- Review of cases and estimated incidence
- Non-clinical and clinical study results
- Literature searches
- Epidemiological data and post-authorization studies results
- Any other information provided in the context of regulatory procedures or ongoing benefit-risk monitoring if applicable

4- Signal and Risk Evaluation:

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.

The following factors should be considered when determining the importance of each risk:

- **Medical seriousness of the risk, including the impact on individual patients**
- **Its frequency, predictability, preventability, and reversibility**

An evaluation of all signals closed during the reporting interval

- Those signals that, following evaluation, have been **refuted as —false signals** based on medical judgment and scientific evaluation of the currently available information, MAH evaluations and conclusions for refuted signals should be supported by data and clearly presented.
- Those signals that, following evaluation, have **been categorized as either a potential or identified risk**, including lack of efficacy

An evaluation of new information that doesn't constitute as signal with respect to previously recognized identified and potential risks (whether important or not).

- **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. It should also include any update on missing information.** In addition, any new information on populations exposed or data generated to address previously missing information should be critically assessed in this sub-section.

Characterization of important potential and identified risks based on **cumulative data** (i.e., not restricted to the reporting interval), and describe missing information.

- Describes the characteristics of the important risks including frequency, number of cases, seriousness, severity, risk factors, preventability, reversibility, public health impact.
- It can remain unchanged across PBRERs, if the new information didn't change the characteristics of risks

A summary of the effectiveness of risk minimization activities

- Risk minimization activities may consist of routine risk minimization (e.g., product labelling) 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
- **Measuring the effectiveness of risk minimization measures through reporting rates is acceptable provided that the MAH is actually collecting ICSRs and in case of PV system failure to collect ICSRs, such method will not be accepted and the MAH should use more structured method to measure the effectiveness**
- Refer to EMA GVP Module XVI for different methods for measuring the effectiveness of risk minimization measures, it addendum I – Educational materials, and any further updates.
- In addition, in all ways the MAH should be capable of collecting ICSRs according to PV requirements under Module VI in EMA GVP

5- Benefit Evaluation

Summarize information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval and provides the basis for the benefit evaluation.

- This information should relate to authorized indication(s) of the medicinal product listed in the reference product information
- For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterized separately by these factors when relevant.

For some products, additional information on efficacy or effectiveness in **authorized indications** may have become available during the reporting interval. Such information should be presented. Information on indications newly authorized during the reporting interval should also be included.

> **Note:** New information on efficacy and effectiveness in uses other than the authorized indications should not be included unless relevant for the benefit-risk evaluation in the authorized indications.

Integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications, providing critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness.

6- 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 should 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 should be presented by population, if possible.

The benefit-risk evaluation should take into account the following points:

- The context of use of the medicinal 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).
- The key benefits and risks considered in the evaluation should be specified & integrated in the benefit risk evaluation.
- 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.
- Key risks, 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 should be considered when formulating the benefit-risk evaluation.

7- Conclusions and actions

The PBRER must be able to answer the following questions:

- **Is there a change in the benefit risk balance?**
- **Is a label update needed?**
- **Are new PV activities or risk minimization measures needed?**
- **Is the benefit risk balance still favorable?**

➢ **<u>Egyptian appendix:</u>**

1- Subsection "Current national product information"

This section should contain a clean copy of the national product information approved in Egypt concerned and which is in effect at the end of the reporting interval.

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 should be prepared by the company, describing these local differences with track change version.

2- Subsection "Proposed product information"

3- Subsection "Proposed additional pharmacovigilance and risk minimization activities"

This sub-section should 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.

4- 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 should be included in this PBRER sub-section. This table should be extracted from the version of RMP available at the beginning of the PBRER reporting interval

5- Subsection "Worldwide marketing authorization status table"

In addition to PBRER section worldwide marketing authorization status, a cumulative table with the following information should 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 medicinal 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 & International companies, the National appendix should include the following:

- Sales data and interval patient exposure in Egypt (for each year of the reporting interval separately if the PBRER covers more than 1 year).
- Data in summary tabulations in Egypt during the reporting interval (in a table organized by MedDRA SOC) & the number of cases reported in Egypt during the PBRER interval.

➢ **General comments:**

Multiple MAH functions contribute to the preparation of PBRERs

A dedicated template with detailed guidance for each function is helpful to obtain complete contribution in good quality.

The title page must be signed and include a statement of confidentiality of the information included in the PBRER.

MAH should 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 concerns should be submitted with the PBRER and assessed in parallel.

During PV inspections:

- Consistency between case reports in safety database and PBRER
- Tracked & documented processes and QC for PBRER & its regulatory submission
- Documented evidence of completion of the actions/changes reported within the PBRER

- **PBRER amendments:**

MAH should adequately revise all requirements and fulfill all pharmaceutical vigilance general administration's comments. Taking into consideration the time consumed in assessing documents with repeated mistakes, this will reflect a negative impression that will be taken about MAH compliance and its Pharmacovigilance system efficiency.

8 Signal Management

8.1 Introduction

This chapter provides terminologies and definitions concerning signal management process, and general guidance and principles on 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 Pharmaceutical Vigilance General Administration.

MAHs may follow alternative signal management processes and terminologies but they should encompass the general principles outlined in this guidance.

The following documents provide additional guidance relevant to signal management activities defined in this Module:

- European Medicines Agency (EMA). EU GVP Module 10 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).

Definitions and terminology

Signal. It is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

According to the EMA, signal id defined 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 medicinal products containing the same active substance, including combination products. Some signals may only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of medicinal 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 medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The Pharmaceutical Vigilance General Administration`s signal management process includes the following activities: signal detection, prioritization, signal validation, signal assessment and

confirmation, recommendation 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 medicinal products as per the applicable regulations and well-established international guidelines.

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 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 patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal 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 should take into account the strength of the evidence, the previous awareness of the association and the clinical relevance (see subsection 10.B.3.). 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 medicinal product or whether known risks have changed. This review may include nonclinical and clinical data and should be as comprehensive as possible regarding the sources of information.

Signal status. 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' or 'non-validated – other'.

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'.

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'.

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 medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Medicinal 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.

8.2 Structures and processes

This subsection provides guidance on sources of data and information, methodology for signal detection, signal validation and further assessment, signal prioritization, and signal quality requirements, refer to EMA GVP Module IX.B

8.3 Operation of Signal management in Egypt

This subsection defines the roles and responsibilities of stakeholders concerned with this this guideline, signal confirmation and further assessment by the pharmaceutical vigilance central administration, notifications and procedural options for validated signals by MAHs, emerging safety issues in signals, inclusion of signal ins PBRER, recommendation for actions, and signal record management. For detailed guidance, refer to EMA GVP module IX.C

Special considerations in Egypt:

- **Roles and responsibilities of the marketing authorization holder operating**

In the context of signal detection and management requirements, the marketing authorization holder should continuously monitor the safety of its medicinal products and inform pharmaceutical vigilance general administration 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 should 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;
- Should detect signals from any sources and subsequently handle them according to the its own signal management process, taking into account the general principles outlined in previously. Validated signals should be notified to pharmaceutical vigilance general administration in a timely manner, taking into account the requirements on the MAH to keep their product safety profile up-to-date throughout the product's lifecycle in the light of latest scientific knowledge and to present comprehensive signal information in PBRERs.

- Shall validate any detected signal and notify pharmaceutical vigilance general administration with the validated or confirmed signals according to the timelines mentioned in this guidance. The MAH should be taken into account the essentials for validating the detected signals;
- Should notify signals that have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health (i.e. meeting the definition of emerging safety issues) to pharmaceutical vigilance general administration in accordance with this guidance.
- Shall collaborate with pharmaceutical vigilance general administration for the assessment of the validated signals by providing supplementary data upon request.
- Shall evaluate the effectiveness of the additional risk minimization measures imposed on its medicinal products post-signal assessment steps and shall inform pharmaceutical vigilance general administration with results upon request.
- Should keep and maintain an audit trail for its signal detection and management activities.

- **Roles and responsibilities of pharmaceutical vigilance general administration being the national pharmacovigilance center and regulator in Egypt**

Pharmaceutical vigilance general administration shall continuously monitor the safety of active substances/medicinal 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 should 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 significant misuse, abuse or 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, 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 product indicated for use in a new patient population or with a new route of administration, or any product containing new innovated active substances authorized for emergency use;
- 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, Pharmaceutical Vigilance General Administration shall take the appropriate regulatory actions following the signal assessment to maintain the positive benefit-risk ratio of medicinal products authorized at the local market.

In specific situations, Pharmaceutical Vigilance General Administration 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 medicinal 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 the EDA;

Pharmaceutical Vigilance General Administration should collaborate with the concerned marketing authorization holder(s) by requesting supplementary data and inform them of the conclusions and outcomes of the assessment of any confirmed signal.

Pharmaceutical Vigilance General Administration shall monitor the PV practice of concerned MAHs in implementing additional risk minimization measures imposed on their medicinal products after signal assessment and confirmation. Additionally, Pharmaceutical Vigilance General Administration should evaluate the extent of effectiveness for the implemented additional risk minimization measures by concerned MAHs and take the necessary actions as needed.

Pharmaceutical Vigilance General Administration should perform a regular review of its signal management methodology in accordance with the latest well-respected international guidelines and best practices and scientific knowledge in relation to causality assessment methods and signal management activities.

Pharmaceutical Vigilance General Administration should keep and maintain a signal tracker for its signal detection and management activities, including, validated signals that require further assessment.

- **Signal confirmation and further assessment by Pharmaceutical Vigilance General Administration**

Pharmaceutical vigilance general administration has the responsibility to confirm in a timely manner the validated signals originated from the domestic ICSRs captured in Vigiflow or other validated signals formerly triggered from any other source when further signal assessment is warranted. Pharmaceutical vigilance general administration may further adjust the signal scope by extending it to other active substances of the same class of medicinal products, other medicinal products for active substances of different pharmacological classes or to other related adverse reactions/medical conditions. templates for pharmaceutical vigilance general administration's signal evaluation reports (new/follow-up signal) should be in place.

The assigned signal assessor should comprehensively evaluate, propose recommendation for action(s), present signal in-depth assessment results on the EDA's PV committee and communicate decisions to the concerned MAH(s), as appropriate.

Marketing authorization holders shall collaborate with pharmaceutical vigilance general administration for the purpose of confirming and in-depth assessing the validated signals. This is by concerned MAH addressing to pharmaceutical vigilance general administration requests for supplementary data. 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 guidance.

Pharmaceutical vigilance general administration 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) should submit the required supplementary data through the proper pharmaceutical vigilance general administration's reception portal specified for such purposes. If a MAH is unable to provide the requested data on time, it shall inform 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 should be provided and a new submission date proposed.

It should take into account that pharmaceutical vigilance general administration may request from MAH(s) of the innovator products such additional information as they are expected to hold the most comprehensive safety data on the concerned active substance.

- **Notifications and procedural options for validated signals by a marketing authorization holder based on the continuous monitoring of PV data from any source**

Standalone signal notification

When a marketing authorization holder based on its preliminary assessment of a signal for an authorized medicinal product detected from any data source and does not meet the criteria outlined in this subsection, 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'), the MAH should submit a standalone signal notification according to the mechanisms of notification listed in Table 1.

A standalone signal notification should be sent after the MAH has validated the detected signal within a timeline no later than 30 calendar days. The MAH should sent to pharmaceutical vigilance general administration a follow-up notification within a timeline no later than 30 calendar days upon completion signal assessment regardless the final concluded status (confirmed/indeterminate/refuted). MAHs should submit their 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 attachments, as appropriate.

Emerging safety issue (ESI) signals

All validated signals that detected from any source and meet the definition of emerging safety issues (ESI) – including quality defects with/without clinical consequences – and require urgent attention, shall only be reported by the MAH as emerging safety issues to the relevant pharmaceutical vigilance general administration reception portal in accordance with the timeline stated (no later than 5 working days). This is in addition to the ICSR submission requirements, when the emerging safety issue refers to a single case of suspected adverse reactions.

When notifying an ESI, the MAH should describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and should provide any relevant documentation available at the time of initial notification. Any further information relevant to the issue should be provided to pharmaceutical vigilance general administration as soon as it becomes available. The MAH should collaborate with PHARMACEUTICAL VIGILANCE GENERAL ADMINISTRATION in the assessment of the emerging safety issue.

For detailed PV requirements in relation to processing of emerging safety issues, refer to chapter 10 in this guidance.

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 pharmaceutical vigilance general administration'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).

Inclusion of the signal in the Periodic Benefit Risk Evaluation Report (PBRER)

If the PBRER of a medicinal product – included in the list of union reference dates and frequency of submission of periodic safety update reports (PBRERs) (known as 'EURD List') – containing an active substance of a validated/confirmed signal is due to be submitted within 6 months from the date of completing corresponding validation/in-depth signal assessment, the submission of a separate standalone signal notification is not required. Alternatively, the associated signal evaluation report (SER) should be provided in the submitted product PBRER.

For medicinal products that are not included in EURD list, the MAH shall comply with the timelines defined in the local PBRER list of local medicinal products which is published on the EDA website.

If there is a validated/confirmed signal for any of the active substances included in the local PBRER list and its due time to be submitted within 6 months from the date of completing corresponding validation/in-depth signal assessment, the submission of a separate standalone signal notification is **NOT** required. Alternatively, the associated signal evaluation report (SER) should be provided in the submitted product PBRER.

Irrespective of the signal detection source, all validated signals and emerging safety issue signals for which the evaluation was concluded during the reporting interval of a PBRER, or are ongoing at the time of a PBRER data lock point, should be reported in that PBRER's 'sections 15 and 16'.

If the data-lock point of the PBRER has elapsed by the time the marketing authorization holder has completed their assessment of the signal, it should be mentioned in the PBRER section 'Late breaking Information' together with a proposal for further management of the signal (see Module VII). As appropriate, pharmaceutical vigilance general administration will further assess within its PBRER process or its routine signal management process.

Based on the evaluation of the cumulative safety data and the risk-benefit balance analysis submitted in the PBRER, the MAH shall draw conclusions regarding the need for changes to the terms of the marketing authorization and/or actions, including any implications for the approved product information for the medicinal product(s) for which the PBRER has been submitted. This also applies to the conclusions drawn based on the evaluation of safety signals.

Recommendation for actions on signals from pharmaceutical vigilance general administration

Pharmaceutical vigilance general administration recommendations for actions are adopted after a comprehensive assessment of validated signals and after discussion by the EDA's pharmacovigilance committee (the 'PV committee'). The decisions may include any or a combination of the following actions:

- The MAH should provide supplementary data (e.g. comprehensive signal evaluation report with/without specific assessment considerations) within a signal procedure;
- The MAH should provide an additional data (e.g. cumulative review) on the signal in the following PBRER or submit an ad-hoc PBRER
- The MAH should update the product safety information according to the applicable regulations for variation procedures by referral to requirements imposed by the pharmacology committee of the Egyptian drug authority;
- The MAH should be requested to submit an updated risk management plan (RMP) for the authorized medicinal product
- The MAH should implement additional risk minimization measures such as local distribution of educational materials or the dissemination of a direct healthcare professional communication (DHPC)
- The MAH should sponsor a post-authorization study according to an agreed protocol and submit the final results of that study
- Other EDA scientific committees or higher technical committees shall be consulted to adopt PV committee recommendations (e.g. adding products containing a specific active

pharmaceutical ingredient (API) into the list of controlled substances, suspension of product authorization or use, market withdrawal, restriction of product administration to specific indication, patient sub-population, or route of administration, etc.)

- The national causality committee (NCC) of the Egyptian ministry of health and population (MoHP) should be consulted to adopt pharmaceutical vigilance general administration recommendations for AEFI signals of vaccines under the umbrella of the national Expanded Program on Immunization (EPI).
- A pharmacovigilance inspection should take place in order to verify that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements as endorsed by the applicable laws, decrees and related regulations
- Pharmaceutical vigilance general administration should collect further information from relevant stakeholders inside the 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 of time, pharmaceutical vigilance general administration can independently request from the concerned MAHs a supplementary data in the context of its routine signal procedures. As appropriate, pharmaceutical vigilance general administration can directly endorse and communicate regulatory actions to a concerned MAH or endorse penalties based on MAH's PV malpractices within the scope of signal management requirements.

Signal record management in Egypt

pharmaceutical vigilance general administration as being the responsible entity of the national pharmacovigilance (PV) system and PV regulations within the Egyptian drug authority (EDA) should 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. Pharmaceutical vigilance general administration 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, the relevant inquiries and their outcomes, as appropriate.

Table 1. Mechanisms of flow for standalone signal notifications received from marketing authorization holders' regardless of the source of signal detection. If the notified signal has met the criteria outlined in ESI or PBRER, no standalone signal notification is required.

Domestic ICSRs	MAH's product type	Registered in reference country?	Signal status	Exchange of information with pharmaceutical vigilance general administration	Timelines
No domestic cases	Innovator Biosimilar Generics	Yes/No	Validated	MAH shall submit a notification on pharmaceutical vigilance general administration's standalone signal notification portal. MAH will receive a confirmation email only for the filled-out submission form.	No later than a month (30 calendar days) from signal validation date

				No further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	
No domestic cases	Innovator Biosimilar Generics	Yes/No	Completed signal assessment [Confirmed/Monitor/Refuted]	MAH shall submit a follow-up notification on pharmaceutical vigilance general administration's standalone signal notification portal. MAH will receive a confirmation email only for the filled-out submission form. no further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	No later than a month (30 calendar days) from date of completed signal assessment
Domestic case(s) available	Generics	Yes/No	Validated	MAH shall submit a notification on pharmaceutical vigilance general administration's standalone signal notification portal. MAH will receive a confirmation email only for the filled-out submission form. No further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	No later than a month (30 calendar days) from signal validation date
Domestic case(s) available	Generics	Yes/No	Completed signal assessment [Confirmed/Monitor/Refuted]	MAH shall submit a follow-up notification on pharmaceutical vigilance general administration's standalone signal notification portal.	No later than a month (30 calendar days) from signal validation date

				MAH will receive a confirmation email only for the filled-out submission form. No further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	
Domestic case(s) available	Innovator Biosimilar	Yes	Validated	MAH shall submit a notification on pharmaceutical vigilance general administration's standalone signal notification portal. MAH will receive a confirmation email only for the filled-out submission form. No further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	No later than a month (30 calendar days) from signal validation date
Domestic case(s) available	Innovator Biosimilar	Yes	Completed signal assessment [Confirmed/Monitor/Refuted]	MAH shall submit a follow-up notification on pharmaceutical vigilance general administration's standalone signal notification portal. MAH will receive a confirmation email only for the filled-out submission form. No further replies from pharmaceutical vigilance general administration will be sent to MAH unless supplementary data is required.	No later than a month (30 calendar days) from signal validation date
Domestic case(s) available	Innovator Biosimilar	No	Validated	MAH shall submit a notification on pharmaceutical vigilance general	No later than a month (30 calendar

				administration's standalone signal notification portal. MAH will receive a confirmation email for the filled-out submission form. pharmaceutical vigilance general administration will send to the MAH a "RECEIPT" e-mail within 5 business days from receiving this type of signal notification. Further pharmaceutical vigilance general administration communication will be sent to MAH.	days) from signal validation date
Domestic case(s) available	Innovator Biosimilar	No	Completed signal assessment [Confirmed/Monitor/Refuted]	MAH shall submit a follow-up notification on pharmaceutical vigilance general administration's standalone signal notification portal. The associated signal evaluation report (SER) should be provided during the submission process of standalone signal notification on pharmaceutical vigilance general administration reception portal. MAH will receive a confirmation email for the filled-out submission form pharmaceutical vigilance general administration will send to the MAH a "RECEIPT" e-mail within 5 business days from receiving	No later than a month (30 calendar days) from signal validation date

				this type of signal notification. Further pharmaceutical vigilance general administration communication will be sent to MAH.	

9 Post authorization Safety Studies

9.1 Introduction

A post-authorization safety study (PASS) is defined as any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of 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 the 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 medicinal 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 medicinal 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 the EDA.
- Describe procedures whereby medicines authorities 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.

9.2 Structures and processes

This section provides guidance on the PASS principles, study registration, study protocol, reporting of PV data to the EDA, publication of study results, data protection, quality system, audits, inspections, and impact on the risk management system. For detailed guidance refer to EMA GVP module VIII.B.

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. For detailed guidance refer to EMA GVP module VIII.C

10 Safety communication

10.1 Introduction

This chapter provides on how to communicate and coordinate safety information concerning medicinal 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) and public assessment reports.

For detailed guidance, refer to EMA GVP module XV, and any recent updates.

10.2 Structures and processes

Safety communication aims at:

1. Providing timely, evidence-based information on the safe and effective use of medicines;
2. Facilitating changes to healthcare practices (including self-medication practices) where necessary;
3. Changing attitudes, decisions and behaviors in relation to the use of medicines;
4. supporting risk minimization behavior;
5. 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

This section provides guidance on the objectives of safety communication, principles of safety communication, target audiences, content of safety communication, means of safety communication, effectiveness of safety communication, and quality system requirements for safety communication. For detailed guidance, refer to EMA GVP XV.B module.

10.3 Operation in Egypt

A good level of coordination of safety communication in Egypt is of particular importance so that healthcare professionals and patients receive consistent information on regulatory decisions. When issuing safety announcements, EDA may make use of the different tools and channels described.

It is recommended that safety announcements to be done in cooperation with the concerned marketing authorization holder(s). Whenever possible, the national medicines authorities recommended to 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.

For detailed guidance on requirements for MAHs, consideration for third parties (e.g. scientific journals, learned societies, patients' organizations), processing of DHPC, translation of DHPC, and publication of DHPC, refer to EMA GVP module XV.C

Special consideration in Egypt:

- **Emerging Safety issue**

A safety issue considered by a marketing authorization holder to require urgent attention by the EDA because of the potential major impact on the risk-benefit balance of the medicinal 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:

• 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 medicinal product or its withdrawal from the market;

• Major safety-related regulatory actions outside Egypt, e.g. a restriction of use of a medicinal 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 medicinal product, are not to be submitted as ICSRs. They should be notified as Emerging Safety Issues in writing to EDA; this should be done immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorization for the concerned medicinal product. Those safety issues should also be analyzed in the relevant sections of the periodic safety update report of the authorized medicinal product.

- **Timing of DHPC notification**

Primary notification of Emerging safety issues and Direct Health Care Professional Communication (DHPC) as soon as possible and **no later than 5 working days.**

- **DHPC**

A direct healthcare professional communication (DHPC) is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorization holder or a medicines authority (in special cases), to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimization activities.

The preparation of DHPCs involves cooperation between the marketing authorization holder and the pharmaceutical vigilance general administration. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorization holder. The agreement will cover both the content of the information and the communication plan, including the intended recipients, the timetable for disseminating the DHPC and the dissemination mechanism.

Where there are several marketing authorization holders of the same active substance for which a DHPC is to be issued; a single consistent message should normally be delivered.

A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply. A DHPC may be an additional risk minimization measure as part of a risk management plan.

A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal 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 should be considered are:
    1. New major warnings or precautions for use in the product information;
    2. New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
    3. Substantiated knowledge that the medicinal product is not as effective as previously considered;
    4. New recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;
    5. 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 should 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 (in special cases) or request the marketing authorization holder to disseminate a DHPC in any situation where the national medicines authority considers it necessary for the continued safe and effective use of a medicinal product.

It is the responsibility of the applicant to ensure that this information is immediately submitted to EDA where the application is under assessment.

In case of under-registration products, the marketing authorization holder should notify the emerging safety issues team about the issue and have to submit a declaration letter that the DHPC will be submitted after marketing of the product or submitting the SmPC accredited containing the risk.

For emerging safety issues in term of signal management: refer to EU (GVP) Module X – Signal management X.C.2. Emerging safety issue

11 Annex I: Definition

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem

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 medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal 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."

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."

Medicinal 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.

Missing information

Gaps in knowledge about the safety of a medicinal 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 should 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."

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' or 'Non-validated – other'.

Pharmacovigilance system

It is a system used by the marketing authorization holder and by the Egyptian Drug Authority (EDA) to fulfill the tasks and responsibilities listed in this guideline and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance.

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal 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 medicinal product."

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 medicinal 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 should it occur. "

Routine pharmacovigilance activities

Routine pharmacovigilance is the primary/minimum set of activities required for all medicinal products and should 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 medicinal product or whether known risks have changed. This review may include nonclinical and clinical data and should be as comprehensive as possible regarding the sources of information.

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 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 medicinal 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 medicinal product and thus require careful attention and management.

Signal status

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

It is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Target population (treatment)

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information"

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'.

For more definitions, refer to EMA GVP Annex I. Definitions.

12 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 medicinal 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 Center for Pharmacovigilance

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 medicinal 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)
PSUR	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

13 Annex III: Templates

13.1 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 medicinal products to which this Egyptian display of RMP refers (i.e. number in the Arab Country concerned):	Choose one of the following: 1 2 3 4 5 6
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

Provide here the table of content of the Egyptian display of RMP and its annexes (hyperlink) as showing the page number

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 medicinal 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 medicinal 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.*

MAH/Applicants having EU RMP in place submit both of the following:

1. *the most updated version of the EU/global RMP (referenced EU/global RMP including its annexes); altogether with*
2. *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 should 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 should 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 medicinal product
	Proposed (if applicable) **in Egypt**
	That of the reference medicinal product
Posology and route of administration in the Arab Country concerned	Current (if applicable) **in Egypt**
	Current of the reference medicinal product
	Proposed (if applicable) **in Egypt**
	That of the reference medicinal product
Pharmaceutical form(s) and strengths	Current (if applicable) **in Egypt**
	Current of the reference medicinal product
	Proposed (if applicable) **in Egypt**
	That of the reference medicinal 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 should summarize all the activities stated in the referenced EU/global RMP, separate table for each medicinal product included in the Egyptian Display of RMP may be provided as appropriate. It should 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 should 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 should be displayed in comparison with those proposed by the MAH/Applicant to be implemented in Egypt; any difference should 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	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	Justification

a) If the MAH/Applicant proposes **not to implement** in Egypt, any of the **activities** stated in the referenced RMP; this should be clearly highlighted in the above table and comprehensive justification should be supplied, in addition explanation of how the safety concern intended by this activity will then be managed in Egypt.

b) 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 should be clearly highlighted in the table and comprehensive justification should be supplied as well.

III.2. *Supplementary activities on the national level*

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 should be presented in details according to the below tables (for details see Module V), as appropriate **any relevant documents should 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 should be described in the above table.

a) Supplementary national 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 should be mentioned and a mock up provided in this Egyptian Display of RMP annex 7. If the supplementary activity(s) is of additional pharmacovigilance type (i.e. additional pharmacovigilance activity); fill in the following table, and protocols should be provided in Annex 6 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 national post-authorization efficacy study(s)

If the supplementary activity(s) is a post-authorization study fill in the following table. The protocols should be provided in Annex 8 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 national 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 should be provided in Annexes 10& 11 of this Egyptian display of RMP.

Safety concern	
Objective(s) of the risk minimization measures	

Safety concern	
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 should 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 should 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

Provide here a list of the annexes of the Egyptian Display of the RMP

List of annexes of the Egyptian Display of RMP

Annex 1 – should submitted only upon request by Egypt
Annex 2 - SmPC & Package Leaflet
Annex 3 - N.A. (submitted already in the referenced RMP)
Annex 4 - N.A. (submitted already in the referenced RMP)
Annex 5 - N.A. (submitted already in the referenced RMP)
Annex 6 - Protocols for proposed & ongoing supplementary additional pharmacovigilance activities in Egyptian Display of RMP section III.2.a (if applicable)
Annex 7 - Specific adverse event follow-up forms section III. 2.a (if applicable)
Annex 8 - Protocols for proposed and ongoing studies in Egyptian Display of RMP section III.2.b (if applicable)
Annex 9 - Synopsis of newly available study reports in Egyptian display Section III.2.a. & b.
Annex 10 - Details of proposed additional risk minimization measures (if applicable)
Annex 11 - Mock-up of proposed additional risk minimization measures (if applicable)
Annex 12 - Other supporting data (including referenced material)

Annex 2 - SmPC & Package Leaflet

Current (or proposed if product is not authorized) local summary of product characteristics (SmPC) and package leaflet(s) for each product in the RMP.

If multiple versions are included for a product, they should show in which Country(s) they are applicable. In addition, if available, a core SmPC should be provided with an overview of the changes applicable to the SmPC in Egypt.

Annex 6 - Protocols for proposed & ongoing supplementary additional pharmacovigilance activities in Egyptian Display of RMP section III.2.a

Overview of included protocols

Study title	Protocol status *	Version of protocol	Date of protocol version
	Choose one of the following: • Draft • Approved		<Enter a date>

*Draft = not approved

Approved = when agreed by authority as appropriate

Annex 7 - Specific adverse event follow-up forms section III. 2.a

Provide forms

Annex 8 - Protocols for proposed and ongoing studies in Egyptian Display of RMP section III.2.b

Study title	Protocol status *	Version of protocol	Date of protocol version
	Choose one of the following: • Draft • Approved		<Enter a date>

*Draft = not approved

Approved = when agreed by Authority

Annex 9 - Synopsis of newly available study reports in Egyptian display Section III.2.a. & b.

Include the study abstract. For non-interventional studies use the abstract format

Annex 10 - Details of proposed additional risk minimization measures (if applicable)

Annex 11 - Mock-up of proposed additional risk minimization measures (if applicable)

Mock up examples in English of the material provided to healthcare professionals and patients. For those materials directed to patients, in addition to the English version, Arabic translation of the mock up shall be included as well.

Annex 12 - Other supporting data (including referenced material)

Index of included material with regard to the Egyptian Display of RMP

13.2 Annex III.2. 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)>

MEDICINAL PRODUCTS COVERED:

Invented name of the medicinal product(s)	Marketing authorisation number(s)	Date(s) of authorisation *(Underline the International Birth Date)*	Marketing authorisation 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 AUTHORISATION HOLDER'S NAME AND ADDRESS:

<Name>
<Address>
<E-mail address> **(contact person for the PSUR procedure)**

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>
<Address>
<Telephone number>
<Fax number>
<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>

<Date>

<Active substance, name of medicinal 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 should 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 the national medicines authority, 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/national medicines authority, if applicable>

Further information

<Link/reference to other available relevant information, such as information on the website of a national medicines authority>

<Therapeutic indication of the medicinal 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

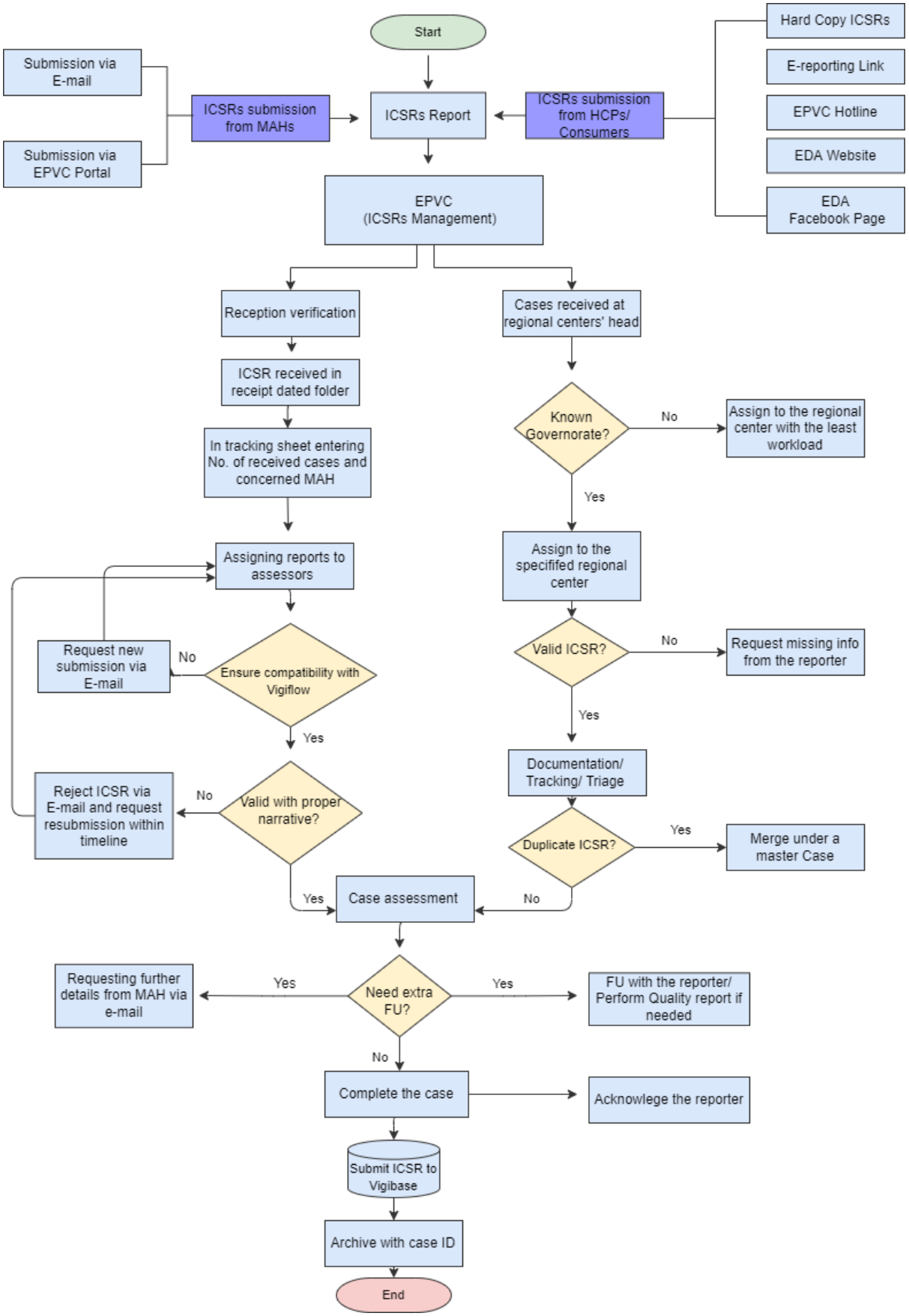
<Relevant sections of the Product Information that have been revised (with changes made visible)>

<Detailed scientific information, if necessary>

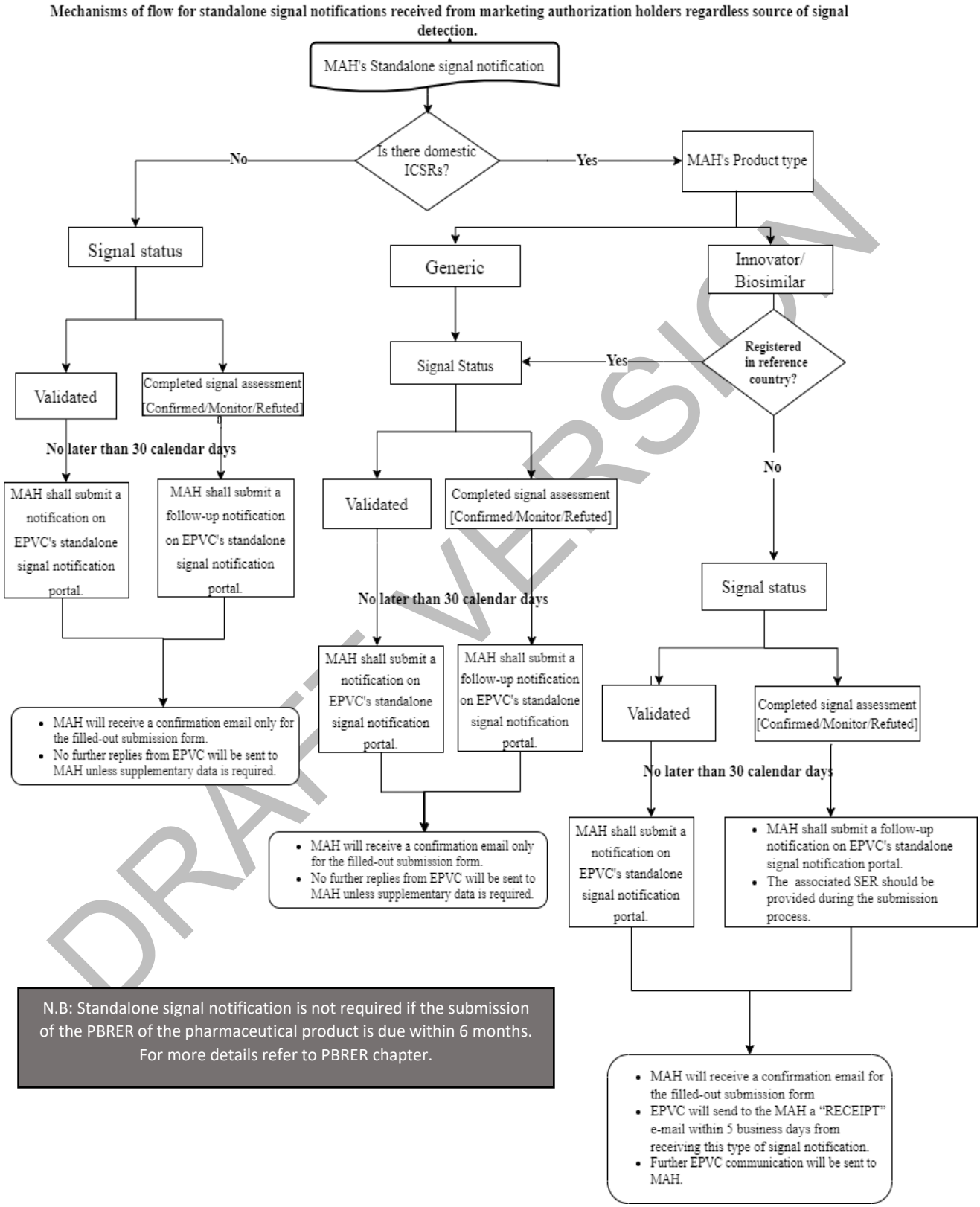
<List of literature references, if applicable>

14 Annex IV: Flowchart

14.1 Flow chart for ICSR management



14.2 Flow chart for signal notification to EDA



15 References

This Guideline is adopted from EMA guidelines for GVP, other resources were referenced as well, such as the ICH and the WHO for the GVP.